RENAL ARTERY STENOSIS:

DIAGNOSTIC STRATEGY AND TREATMENT

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DIAGNOSTISCHE STRATEGIE EN BEHANDELING

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Aan mijn ouders

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CHAPTER 1

INTRODUCTION

INTRODUCTION

If essential hypertension is a disease of theories, then renovascular hypertension is a disease of experiments.[1] No other form of experimental hypertension has been more widely studied. The pathophysiology of renovascular hypertension is known in great detail. The question, however, of how to translate the experimental knowledge into clinical practice is a different matter, and the answer is far from clear. The main difficulty is that renovascular hypertension in experimental animals is not the same as hypertension associated with renal artery stenosis in humans. Renal artery stenosis in humans is in most cases caused by atherosclerosis, a progressive disease quite different from the silver clip in experimental animals. In the kidney, atherosclerosis does not only affect the large arteries but also the small arteries and arterioles. Furthermore, atherosclerosis is not limited to the kidney, it also affects the heart and the brain. There is no cure for atherosclerosis; restenosis after angioplasty is still a daunting problem. Finally, renal artery stenosis can be a complication of essential hypertension or essential hypertension can coincide with renovascular hypertension.

Renal artery stenosis may cause severe and refractory hypertension and it frequently does so.[1] This will lead to multiple organ damage such as hypertensive retinopathy, left ventricular hypertrophy, coronary vascular disease, heart failure and cerebrovascular accident.[2] Progression of renal artery stenosis to renal artery occlusion results in loss of kidney function, and, in case of bilateral renal artery involvement or in the presence of atherosclerotic disease of smaller renal arteries, it will lead to end-stage renal failure.[3-8]

Epidemiology

The prevalence of renal artery stenosis is estimated to be less than 1% of the general hypertensive population,[9] but hypertension is common and renal artery stenosis is therefore not rare. In the Netherlands, the prevalence of hypertension is approximately 20%.[9] When the prevalence of renal artery stenosis is 1%, this would result in about 30.000 patients with renal artery stenosis. The contribution of renovascular disease to the incidence of end-

stage renal failure in the Netherlands was estimated at 13% in 1987 and 21% in 1997.[10] These figures, however, include both macrovascular disease (atherosclerotic renal artery stenosis and fibromuscular dysplasia) and intrarenal vascular disease. On the other hand, in patients with hypertension and renal failure, clinical tests to diagnose renal artery stenosis are often omitted. The reasons for this are a pessimistic view with regard to the reversibility of renal failure after angioplasty, and the fear of further deterioration of renal function by renal angiography due to radiocontrast nephrotoxicity. With increasing age of the population in the near future the incidence of atherosclerotic vascular disease will also increase. It is remarkable that so little solid data are available on the true consequences of renovascular disease in terms of renal function impairment. Predictions on cost-efficiency of screening methods are therefore difficult.[11]

The gold standard for the diagnosis renal artery stenosis is renal angiography. This is an invasive procedure with a risk of anaphylactic reactions and nephrotoxicity.[12-14] This, combined with the low prevalence of renal artery stenosis in the general population of hypertensive patients, form the rationale for the continuing search for a reliable non-invasive screening test. The specificity of such a test has to be very high in order to keep the number of false-positive results as low as possible. Even with a test that has 90% specificity and 90% sensitivity, less than a quarter of patients with a positive test will indeed have renal artery stenosis (positive predictive value). It will be very difficult - if not impossible - to develop a diagnostic test with such high accuracy.

Diagnostic procedures

Renal scintigraphy is the most widely recommended screening test for renal artery stenosis. The procedure consists of the intravenous administration of a radiopharmacon that is exclusively eliminated by the kidney. Depending on the type of radiopharmacon, it may be cleared by glomerular filtration or by both filtration and excretion. Over the years, many modifications of this technique have been described, reporting sensitivities varying from 60% to 100%.[15-30]

Because the usefulness of a diagnostic test depends on the prevalence of renal artery stenosis in the population under study, it would be interesting to

identify the factors that influence this prevalence. Previous studies do not offer a systematic approach on this subject. The texbooks report several clinical features, that enhance the chance that a renal artery stenosis is present: onset of hypertension <25 or >45 years, recent diagnosis of hypertension, accelerated hypertension, atherosclerotic vascular disease elsewhere, unexplained pulmonary edema, abdominal bruit and hypertensive retinopathy.[31] Several studies report the prevalence of these clinical characteristics in patients with and without renal artery stenosis,[32-41] but the precise risk of a random patient in the possession of one or several of these characteristics can not be deduced from these data. The most detailed advice how to select a hypertensive patient for angiography based on a clinical estimate of the risk of renal artery stenosis, is presented by Albers and Svetkey.[31] They propose to establish the pretest probability for renovascular hypertension through the application of specified major and minor clinical features and atherosclerotic vascular disease. Still, it is unclear how many patients will be identified and missed by such an approach. Mann and Pickering[42] also suggest a differentiated work-up for patients with a low (<1%), moderate (5-15%) or high (>25%) index of clinical suspicion. Specific characteristics that determine this index of suspicion are described, but no data are provided to prove that they really correspond to the given chances of stenosis.

In most clinical centers, the final diagnosis of renal artery stenosis is made by intra-arterial angiography. The presence of the anatomic lesion alone is insufficient to define the consequences of renal artery stenosis, renovascular hypertension and ischemic renal disease. In addition to the stenosis, a reduction in renal blood flow should be demonstrated with a high systemic renin concentration. Because measurement of renal blood flow and renin concentration is complicated, and because both are influenced by a vast amount of external factors (e.g. salt intake, drug use, hemodynamic status, vascular compliance), the term 'functional significance' is being used to indicate whether the stenosis causes a decrease in blood flow. Various tests were developed to assess this functional significance of a renal artery stenosis, such as the captopril renin challenge test, captopril renal scintigraphy, and renal vein renin sampling. Furthermore, the severity of the obstruction was thought to be of major importance for clinical sequelae to

develop. According to some authors a stenosis must cause at least 50% reduction of the lumen diameter before it can have hemodynamic consequences[31,41,43-47], whereas others set the degree at 60%[48-51] or 70%.[20,25] The fierce discussion on this subject seems to imply that the exact degree of stenosis is an objective finding from the gold standard angiography.

Angioplasty

Initially, surgical revascularization was the only treatment available,[52-54] but due to the high complication rate of surgery a conservative medical approach was advocated for some patients.[55,56] Since the introduction of balloon angioplasty,[57] this procedure (whether or not combined with stent placement) has become the preferred treatment. Probably because balloon angioplasty was conceptually so attractive, a randomized study comparing the technique with drug treatment was never performed. Uncontrolled studies have shown a beneficial effect on hypertension, but these studies have been criticized for various shortcomings.[58] In most studies the effect of angioplasty was judged on single blood pressure measurements before and some time (a not prespecified period) after the procedure. Moreover, the use of antihypertensive drugs was not standardized and was insufficiently accounted for in the analysis of the results. Finally, there was no uniformity between studies in the definition of cure and improvement of hypertension, and these outcome measures were often ambiguously described. Because the variability of blood pressure is notorious, these failings left much room for subjective interpretation of study results.

A second consequence of renal artery stenosis is the effect on renal function. In patients with renal failure due to artery stenosis, improvement of renal function was only shown in part of the patients and only in a non-randomized setting.[59-61] No information is available on the long-term effect of angioplasty on renal function.

Aims of the thesis

This thesis addresses the following questions: (1) What is the optimal diagnostic strategy to identify patients with renal artery stenosis among the general hypertensive population? (2) Is balloon angioplasty in patients with

renal artery stenosis caused by atherosclerosis more effective for the treatment of hypertension than medical treatment alone?

Chapter 2 describes a study of the sensitivity and specificity of renal scintigraphy, comparing different techniques and modifications. In order to study the two above-mentioned questions a multicenter study was designed, the Dutch Renal Artery Stenosis Intervention Cooperative study. The rationale, design and inclusion data of this study are described in **Chapter 3**. The main theme of this study is the selection of patients based on the blood pressure response to generally used antihypertensive drug regimens. In order to objectify the use of antihypertensive drugs and to make comparisons with other drug regimens possible, standardized drug regimens were chosen for treatment of the included patients. The objective of **Chapter 4** was to investigate the usefulness of these standardized regimens for the identification of drug-resistant hypertension as a predictor of renal artery stenosis. A further refinement of this selection method is described in **Chapter 5**. In a multivariate analysis, clinical characteristics were combined in a model predicting the presence of renal artery stenosis. To enable the use of this regression model in clinical practice, a prediction rule was constructed. Renal angiography is generally used as the gold standard for renal artery stenosis. In **Chapter 6** we studied the uniformity of the assessment of angiograms by experienced radiologists. Finally, in **Chapter 7** a randomized study is described comparing the effect of balloon angioplasty on hypertension with the effect of antihypertensive medication in patients with atherosclerotic renal artery stenosis.

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CHAPTER 2

THE PLACE OF RENAL SCINTIGRAPHY IN THE DIAGNOSIS OF RENAL ARTERY STENOSIS: FIFTEEN YEARS OF CLINICAL EXPERIENCE

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ABSTRACT

Background: Renal scintigraphy with radiolabeled diethylene triamine pentaacetic acid (DTPA) or, more recently, mercaptoacetyltriglycine (MAG_3), with or without captopril challenge, is widely recommended as a diagnostic test for renal artery stenosis.

Objectives: To address (1) whether the diagnostic accuracy has been improved by the use of captopril and the introduction of MAG_3 and (2) whether a renal scan that shows abnormalities is a useful criterion to select patients for renal arteriography.

Patients and methods: A standard diagnostic protocol, using both scintigraphy and arteriography, was followed in 505 consecutive high-risk hypertensive patients who were evaluated for renovascular hypertension at the University Hospital Rotterdam, The Netherlands, from 1978 to 1992.

Results: Renal artery stenosis (≥50%) was present in 263 patients. When the single-kidney fractional uptake was used as a diagnostic criterion, a specificity of 0.90 was obtained at a cut-off value of 35% for the worst kidney in DTPA scintigraphy without captopril challenge (n=225) and at a cut-off value of 37% after captopril challenge (n=280). This was associated with sensitivity levels of 0.65 and 0.68, respectively. The difference between DTPA uptake with and without captopril challenge in the 85 patients who were studied under both circumstances, was no more accurate as a predictor of renal artery stenosis. In the 93 patients who were studied with MAG_3 as well as with DTPA, both after captopril challenge, the diagnostic accuracy was no better with MAG_3 than with DTPA; MAG_3 failed to offer any advantage not only when the single-kidney fractional uptake was used as a criterion, but also with the use of other scintigraphic parameters (eg, time to peak (T_{max}), time to pyelum, overall shape of renographic curve, and kidney size).

Conclusions: The diagnostic accuracy of renal scintigraphy has not been improved by the introduction of MAG_3 or by the use of captopril. The usefulness of scintigraphy as a diagnostic test for the presence of renal artery stenosis remains questionable. The physician will always confront either a substantial number of arteriograms that do not show abnormalities when renal scintigraphy is omitted as a screening step or a substantial number of missed diagnoses when a renal scan that shows abnormalities is used as a prerequisite for arteriography.

INTRODUCTION

The place of renal scintigraphy in the diagnosis of renovascular hypertension has been hotly debated. Scintigraphy is thought to be the most reliable noninvasive procedure currently available for predicting the presence of a clinically significant renal artery stenosis.[1-10] A renal scan that shows abnormalities is therefore used as the basis for selecting hypertensive patients who will require further diagnostic work-up with renal arteriography. Clinical experience, however, shows that the predictive value of renal scintigraphy is highly variable, and it depends on the selection of patients, on the criteria by which the renal scans are analyzed, and on the radiopharmaceutical that is used.[8,11-13] In addition, many clinicians believe that in a patient with severe drug-resistant hypertension, particularly when this condition is associated with signs of generalized atherosclerosis, arteriography is warranted irrespective of whether the renal scan shows abnormalities.

During the past 15 years, all patients who were evaluated for renovascular hypertension at our hypertension center underwent both renal scintigraphy and arteriography. Most of these patients had been referred because of severe hypertension that was difficult to treat; some were referred because their hypertension was associated with generalized atherosclerosis or with an abdominal bruit. Our standard practice of always performing arteriography after scintigraphy remained constant during this 15-year period, although the methods that were used to prepare patients for scintigraphy and the scintigraphic procedures were modified in accordance with prevailing recommendations. From 1978 to 1983, technetium 99m-labeled diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) was used for renal scintigraphy. From 1983 to 1990, the angiotensin-converting enzyme (ACE) inhibitor captopril was administered to enhance the diagnostic accuracy of DTPA scintigraphy.[1,2] From 1990 to 1992, ^{99m}Tc-DTPA, which is a marker of glomerular filtration, was gradually replaced by technetium 99m-labeled mercaptoacetyltriglycine (^{99m}Tc-MAG_3), which is a marker of renal blood flow.[12]

Because renal scintigraphy was always followed by renal arteriography in our center, it was possible for us to address the following questions:

(1) Have the sensitivity and specificity of renal scintigraphy been improved by the use of captopril? (2) Have the sensitivity and specificity of scintigraphy been improved by the use of MAG_3 instead of DTPA? (3) Does our experience confirm that a renal scan with abnormalities is a useful criterion for selecting patients for arteriography?

PATIENTS AND METHODS

This study comprised 505 consecutive high-risk hypertensive patients who were referred to the University Hospital Dijkzigt, Rotterdam, The Netherlands, from 1978 to 1992 for evaluation of possible renovascular hypertension. All patients underwent renal scintigraphy and arteriography according to a standard protocol. The reasons for referral were one or more of the following conditions: (1) refractory hypertension (diastolic blood pressure ≥95 mmHg, while receiving three antihypertensive drugs); (2) severe hypertension (diastolic blood pressure ≥110 mmHg that was associated with signs of generalized atherosclerotic disease [coronary heart disease and/or claudication]); (3) severe hypertension before reaching the age of 40 years; (4) the presence of an abdominal bruit; or (5) a rise in the serum creatinine level of 20 μmol/L or greater (≥0.23 mg/dL) during treatment with an ACE inhibitor. The majority of patients had refractory hypertension. None of the patients exhibited evidence of endocrine or renal parenchymal disease. The results of urinalysis and the levels of serum electrolytes, thyrotropin (thyroid stimulating hormone), and plasma catecholamines were normal; the plasma cortisol level showed adequate overnight suppression after dexamethasone. The serum creatinine was greater than 106 μmol/L (>1.2 mg/dL) in 239 patients, and greater than 221 μmol/L (>2.5 mg/dL) in 27 patients.

Our analysis encompassed the following four study groups (**Figure 1**): group 1, DTPA scintigraphy without captopril (n=182); group 2, DTPA scintigraphy both without captopril and following a challenge with 50 mg of captopril at 2 to 8 weeks later (n=85); group 3, DTPA scintigraphy after a challenge with 50 mg captopril (n=145); and group 4, DTPA scintigraphy

and MAG_3 scintigraphy, performed 2 to 8 weeks apart, both after captopril challenge (n=93).

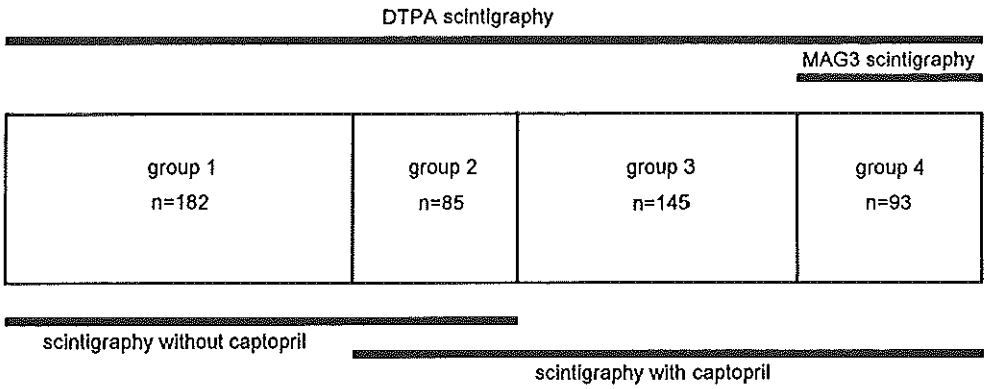

Figure 1. Study groups divided according to scintigraphic procedure.

Scintigraphic procedures and data analysis

In patients who were receiving long-term ACE inhibitor treatment, the ACE inhibitor was withheld for at least 24 hours before scintigraphy was performed. Patients who underwent scintigraphy with captopril challenge received 50 mg of captopril orally at one hour before the examination. To ensure adequate absorption of captopril, patients were required to fast during the 4 hours preceding scintigraphy. Sufficient hydration was guaranteed by the oral administration of 0.5 L of tap water. Blood pressure was measured with an automatic device (Accutorr 1A and 3, Datascope, Datascope Corp, Montvale, NJ, USA) before administration of captopril and every 5 to 10 minutes for 2 hours after administration of captopril.

Scintigraphy was performed with the patient in a supine position, and the detector was placed posteriorly. After intravenous administration of ^{99m}Tc-DTPA or ^{99m}Tc-MAG_3, data were collected in 10-second frames during a 20-minute period, and sequential analog images were obtained every minute. Regions of interest were delineated by the computer, and an area for background correction was placed between the kidneys.[14] The single-kidney contribution to the total renal uptake of the radionuclide, measured during the second minute after injection, was expressed as a percentage of the net total of two-kidney counts (single-kidney fractional uptake). The kidney

with the lowest uptake was considered to be the kidney that was most likely to be affected.

In the patients who were studied with both DTPA and MAG_3 renography, the following criteria other than the single-kidney fractional uptake of radionuclide were also analyzed:[6,14-16] (1) visual assessment of kidney size (normal or small); (2) time until activity appeared in the renal pelvis, determined by visual evaluation of the 1-min sequential images by the nuclear radiologist (time to pyelum); 3) time to peak activity (T_{max} [ie, the time until the maximal amplitude of the renogram was reached]); (4) the overall pattern of the renographic curve; and (5) interpretation by the nuclear radiologist (suspect or not suspect). The receiver operating characteristic (ROC) curves were generated for various parameters of scintigraphy.[17]

Arteriography was performed via the femoral approach. In the vast majority of patients aortography with the digital subtraction technique resulted in adequate visualization of the renal arteries and their main branches. In cases of doubt about the patency of the renal artery, a selective ostial injection of a radiocontrast medium was given. A stenosis was considered to be significant when the diameter of the arterial lumen was reduced by 50% or more. In patients with bilateral renal artery stenosis, the kidney with the most severe stenosis on the arteriogram was referred to as the affected kidney. In the same session in which arteriography was performed, the effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were determined with the continuous infusion method by using ^{131}I-Hippuran and ^{125}I-Thalamate and measuring radioactivity in plasma at the steady state.[18]

Statistical analyses

Data are presented as mean ± standard deviation, or as the medians and ranges, unless stated otherwise. Comparisons of variables with a binomial distribution were made using the chi-square test. Comparisons of variables with a normal distribution were made by Student *t* test and one-way analysis of variance, and comparisons of variables with a skewed distribution were made using the Mann-Whitney *U* test and the Kruskal-Wallis test. Differences in diagnostic performance between DTPA scintigraphy with

and without captopril challenge, and between DTPA and MAG_3 scintigraphy were assessed by comparing the areas under the ROC curves.[19] Two-tailed *P* values less than .05 were considered to indicate statistical significance.

RESULTS

Renal arteriography

Of the total of 505 consecutive patients evaluated for renovascular hypertension, renal artery stenosis was shown on the arteriograms of 263. The remaining patients were considered to have essential hypertension. The prevalence of renal artery stenosis in the four study groups varied from 42% to 55% (**Table 1**). In the overwhelming majority of patients with renal artery stenosis (86%), the stenosis was attributable to atherosclerosis, which was right-sided in 66 patients, left-sided in 81, and bilateral in the remaining 78. Bilateral fibromuscular dysplasia was observed in 16 patients and unilateral dysplasia in 22 patients, 19 of whom showed right-sided localization. There were minor differences in blood pressure, the serum creatinine level, GFR and body mass index (defined as the weight in kilograms divided by the height in meters squared) among the four study groups, but these differences were not important enough to warrant inclusion in our analysis.

In **Table 2**, the key clinical characteristics of the patients with renal artery stenosis are compared with those of the subjects with essential hypertension. As expected, the patients with renal artery stenosis were older, had higher serum creatinine levels, a lower renal plasma flow and a lower GFR. The somewhat higher body mass index in the patients with essential hypertension can be explained by the high prevalence of obesity in patients with severe drug-resistant essential hypertension.[20] The systolic blood pressure was higher in patients with renal artery stenosis, while the diastolic blood pressure was equal in both groups.

The number of serious complications caused by arteriography was small. Renal function impairment (serum creatinine >221 μmol/L [2.5 mg/dL]), which was reversible, was seen in 8 patients. One patient had a hematoma at

Table 1. Characteristics of hypertensive patients who underwent renal scintigraphy and arteriography.*

Characteristics	DTPA scintigraphy without captopril group 1 n=182	DTPA scintigraphy without and after 50 mg captopril group 2 n=85	DTPA scintigraphy after 50 mg captopril group 3 n=145	DTPA and MAG3 scintigraphy after 50 mg captopril group 4 n=93	*P*
Males, %	59	65	62	56	.64
Age, y	51.3 ± 15.1	52.0 ± 12.7	53.9 ± 12.8	52.5 ± 12.8	.39
Body mass index, kg/m²	24.2 ± 4.2	24.8 ± 3.3	24.7 ± 3.5	26.0 ± 5.2	.007
Median serum creatinine level, µmol/L (mg/dL); range	105 (1.19); 62-631 (0.70-7.14)	101 (1.14); 60-269 (0.68-3.04)	120 (1.36); 37-338 (0.42-3.82)	94 (1.06); 62-309 (0.70-3.50)	.005
Serum creatinine level >221 µmol/L (>2.5 mg/dL), no. of patients	15	2	7	3	.14
Blood pressure at referral, mm Hg					
Systolic	190 ± 33	196 ± 26	210 ± 30	212 ± 39	<.001
Diastolic	113 ± 16	115 ± 15	124 ± 19	119 ± 18	<.001
Effective renal plasma flow, mL/min	319 ± 145	335 ± 123	312 ± 126	349 ± 131	.28
Glomerular filtration rate, mL/min	85 ± 25	90 ± 21	79 ± 24	84 ± 43	.04
Patients with renal artery stenosis, %	54	55	54	42	.19

*Plus-minus values are mean ± SD, unless indicated otherwise.

the puncture site that required surgical decompression. One patient suffered from cholesterol crystal embolization, with livedo reticularis in both legs.

Table 2. Characteristics of patients with essential hypertension and renal artery stenosis.*

Characteristics	Essential hypertension n=242	Renal artery stenosis n=263	*P*
Males, %	57	64	.10
Age, y	49.4 ± 12.8	55.1 ± 13.9	<.001
Body mass index, kg/m²	26.0 ± 3.9	23.7 ± 4.0	<.001
Median serum creatinine level,	91 (1.03);	121 (1.37);	
μmol/l (mg/dL); range	37-423 (0.42-4.79)	60-631 (0.68-7.14)	<.001
Blood pressure at referral, mm Hg			
Systolic	194 ± 35	202 ± 30	.02
Diastolic	117 ± 19	116 ± 16	.73
Effective renal plasma flow, mL/m	381 ± 135	272 ± 110	<.001
Glomerular filtration rate, mL/min	93 ± 28	76 ± 24	<.001

*Plus-minus values are mean ± SD, unless indicated otherwise.

Effect of captopril on the renal scan

Between-patient comparison. Results obtained in the subjects who underwent DTPA scintigraphy without captopril challenge were compared with those in the subjects who underwent DTPA scintigraphy after captopril challenge. This analysis included groups 1, 3 and 4, as well as the patients in group 2 who were randomly allocated to group 1 or 3.

In patients with essential hypertension, the single-kidney fractional uptake of DTPA was slightly but significantly lower on the left side than on the right side during scintigraphy without captopril challenge. The fractional uptake of the kidney with the lowest contribution to the total renal uptake was not altered by captopril challenge (**Table 3**). In patients with renal artery stenosis, the single-kidney fractional uptake on the affected side was reduced compared with that in subjects with essential hypertension. The

Table 3. Between-patient comparison of fractional single-kidney uptake in DTPA scintigraphy with and without captopril challenge.*

Type of scintigraphy	Essential hypertension, % contribution			Renal artery stenosis, % contribution		
	Right kidney	Left kidney	Kidney with lowest uptake	Affected	Contralateral kidney	Kidney with lowest uptake
Without captopril challenge (n=225)	53.6 ± 9.1†	46.4 ± 9.1	43.1± 6.9	25.1 ± 17.0‡	74.9± 17.0	24.6 ± 16.4§
After captopril challenge (n=280)	50.9 ± 8.1	49.1 ± 8.1	44.0 ± 5.5	27.8 ± 16.2‡	72.2± 16.2	27.6 ± 16.0§

*Data are mean ± SD. The contribution of the kidney with the lowest uptake without captopril challenge was not significantly different from the contribution after captopril challenge (P = .28 for essential hypertension, P = .14 for renal artery stenosis).
†P<.001 for difference relative fo left kidney.
‡P<.001 for difference relative to contralateral kidney.
§P<.001 for difference relative to essential hypertension.

asymmetry between the two kidneys was therefore increased in patients with renal artery stenosis, but again, the asymmetry was not affected by captopril challenge (Table 3).
The ROC curves were generated for the kidney with the lowest uptake, and the ROC curve for DTPA scintigraphy without captopril challenge was compared with the ROC curve for scintigraphy after captopril challenge (**Figure 2**). There was no difference between the areas under the two curves (0.84 ±0.03 vs 0.84 ±0.02 respectively, mean ±SEM). Because a high specificity is required for the diagnosis of renal artery stenosis, the optimal cut-off point for a positive test was determined as the value that corresponded with a specificity of 0.90. For the whole group, a specificity of 0.90 was obtained at a cut-off value of 35% (single-kidney fractional uptake ≤35% was considered suspect for renal artery stenosis) without captopril challenge, and at a cut-off value of 37% with captopril challenge (**Table 4**).

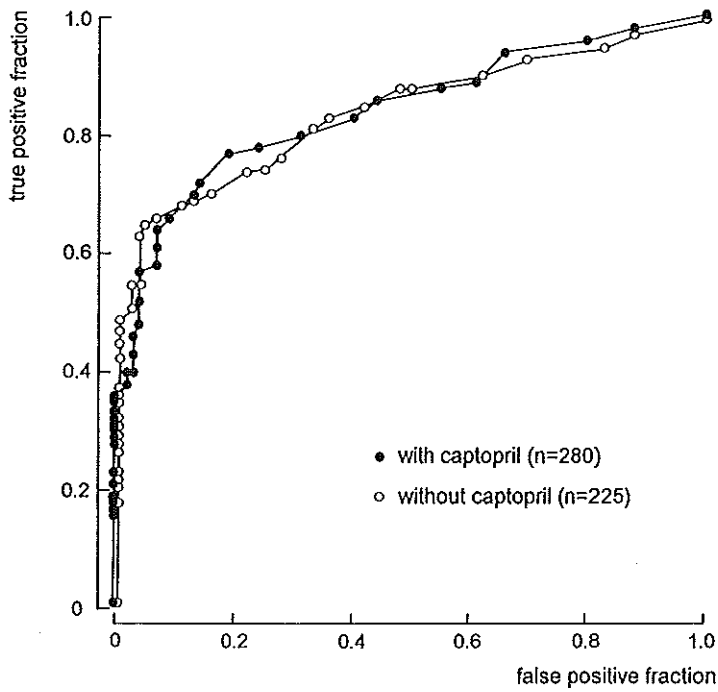

Figure 2. The receiver operating characteristic curves for the single-kidney fractional uptake in DTPA scintigraphy and with and without captopril challenge.

Data were also analyzed separately for unilateral and bilateral stenosis, a decrease in the fractional uptake on the less-affected side after captopril challenge might have obscured the asymmetry between This was associated with a sensitivity of 0.65 and 0.68, respectively. Data were also analyzed separately for unilateral and bilateral stenosis because, in the two kidneys. The sensitivity was indeed somewhat better for unilateral stenosis than for bilateral stenosis, but captopril had little effect on the diagnostic accuracy of DTPA scintigraphy in either group.

Table 4. Between-patient comparison of DTPA scintigraphy with and without captopril challenge.*

Comparison	Captopril challenge	Sensitivity	Specificity	Cut-off value for SKFU
EHT vs RAS	no	0.65	0.90	35%
	yes	0.68	0.90	37%
EHT vs URAS	no	0.70	0.90	35%
	yes	0.73	0.90	37%
EHT vs BIRAS	no	0.63	0.90	35%
	yes	0.58	0.90	38%

* EHT indicates essential hypertension (n=242); RAS, renal artery stenosis (n=263); URAS, unilateral renal artery stenosis (n=169); BIRAS, bilateral renal artery stenosis (n=94);and SKFU, single-kidney fractional uptake.

Within-patient comparison. This analysis was performed in the group of patients who underwent DTPA scintigraphy both without captopril and after captopril challenge (group 2). The kidney with the lowest uptake during DTPA scintigraphy without captopril challenge was compared with the same kidney after captopril challenge. The effect of captopril was analyzed by subtracting the single-kidney fractional uptake of DTPA after captopril challenge from the uptake without captopril challenge. The results are shown in **Figure 3**.

In four patients, the kidney with the lowest uptake contributed 10% or less to the total renal uptake during DTPA scintigraphy without captopril challenge. As expected, captopril did not change the fractional uptake by

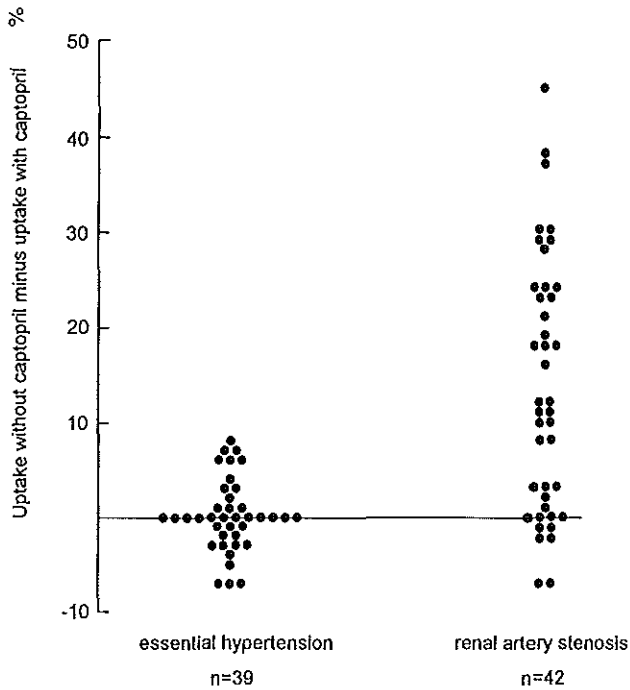

Figure 3. Effect of captopril on single-kidney fractional uptake in DTPA scintigraphy.

these kidneys. These cases were therefore excluded from the analysis presented in Figure 3. The optimal cut-off point for a positive test, corresponding to a specificity of 0.90, was a value of 5% for the difference in fractional uptake between DTPA scintigraphy without captopril challenge and DTPA scintigraphy after captopril challenge, and this was associated with a sensitivity of 0.64. Thus, dual DTPA scintigraphy, in which one renal scan was obtained after captopril challenge and one without, did not offer any advantage over single DTPA scintigraphy either with captopril challenge or without.

It has been well documented that the number of false-negative tests in DTPA scintigraphy can be reduced by the use of captopril.[3,8,21,22] In our series, this was the case in 12 of the 29 patients with unilateral stenosis and in 4 of the 17 patients with bilateral stenosis. However, in 3 patients with unilateral stenosis and in 3 patients with bilateral stenosis, the test remained negative after captopril challenge. Moreover, in some patients with essential

hypertension, the test became positive after captopril challenge, or was positive both with and without captopril challenge. Thus, although the use of captopril can improve the diagnostic accuracy of DTPA scintigraphy in individual cases, this is not a uniform finding; in fact, captopril may increase the number of false-positive tests.

MAG_3 vs DTPA scintigraphy

Between-patient comparison. MAG_3 scintigraphy was always performed after captopril challenge. Results of MAG_3 scintigraphy were therefore compared with those of DTPA scintigraphy after captopril challenge. The analysis includes groups 2, 3, and 4.

A striking difference between the MAG_3 and DTPA scintigrams was the diminished asymmetry between the two kidneys that was observed on the MAG_3 scans in patients with renal artery stenosis (**Table 5**). Again, the ROC curves were generated for the kidney with the lowest uptake. A specificity of 0.90 was obtained at a cut-off value of 35% for the single-kidney fractional uptake both with MAG_3 and DTPA scintigraphy. This specificity was associated with a sensitivity of 0.42 for MAG_3, and 0.69 for DTPA. Thus, when the single-kidney fractional uptake was taken as the test criterion, DTPA scintigraphy was superior to MAG_3 scintigraphy.

Within-patient comparison. This analysis was limited to the patients who underwent MAG_3 scintigraphy as well as DTPA scintigraphy, both after captopril challenge (group 4). A specificity of 0.90 was obtained at a cut-off value of 36% for the single-kidney fractional uptake with MAG_3 scintigraphy and at a cut-off value of 38% with DTPA scintigraphy. This was associated with a sensitivity of 0.42 for MAG_3 and 0.61 for DTPA. These results are similar to those of the larger between-patient analysis.

In the interpretation of MAG_3 scans, parameters other than the single-kidney fractional uptake might be better discriminators for the presence or absence of renal artery stenosis. **Table 6** provides data on the diagnostic accuracy of the single-kidney fractional uptake, as well as other scintigraphic parameters (ie, the time to peak [T_{max}], time to pyelum, overall pattern of the renographic curve, and kidney size), in both MAG_3 scintigraphy and DTPA scintigraphy. These data show that, indeed, with the use of MAG_3, the T_{max} and time to pyelum are better criteria than the single-

Table 5. Between-patient comparison of single-kidney fractional uptake in DTPA and MAG3 scintigraphy*

	Essential hypertension, % contribution			Renal artery stenosis, % contribution		
Type of scintigraphy	Right kidney	Left kidney	Kidney with lowest uptake	Affected kidney	Contralateral kidney	Kidney with lowest uptake
DTPA after captopril n=230	51.4 ± 7.9	48.6 ± 7.9	44.0 ± 5.3	24.4 ± 16.8†	75.6 ± 16.8	24.2 ± 16.5‡
MAG3 after captopril n=93	50.5 ± 9.5	49.5 ± 9.5	43.5 ± 6.9	36.5 ± 12.2†§	63.5 ± 12.2	36.5 ± 12.2‡§

*Data are mean ± SD.
†P<.001 for difference relative to contralateral kidney.
‡P<0.001 for difference relative to essential hypertension.
§P<.001 for difference relative to DTPA scintigraphy.

Table 6. Diagnostic accuracy of various scintigraphic parameters in patients who underwent DTPA as well as MAG3 scintigraphy, both after captopril (n=93).*

	DTPA scintigraphy		MAG3 scintigraphy	
Parameter	Sensitivity	Specificity	Sensitivity	Specificity
Small kidney	0.55	0.76	0.50	0.71
SKFU cut-off value:				
44%	0.79	0.54	0.63	0.65
42%	0.68	0.70	0.50	0.73
40%	0.63	0.85	0.47	0.76
38%	0.61	0.87	0.45	0.82
36%	0.53	0.93	0.42	0.89
TTP cut-off value:				
≥5 min	0.79	0.58	0.74	0.75
≥6 min	0.68	0.86	0.53	0.89
≥7 min	0.68	0.96	0.50	0.98
≥2 min difference†	0.61	0.98	0.47	0.96
Tmax cut-off value:				
≥5 min	0.76	0.53	0.79	0.44
≥6 min	0.68	0.78	0.66	0.67
≥7 min	0.66	0.80	0.63	0.84
≥2 min difference†	0.61	0.87	0.55	0.86
TTP, ≥6 min or difference in Tmax, ≥2 min	0.71	0.76	0.63	0.80
Pattern of renographic curve, curve type ≥2‡	0.66	0.91	0.53	0.89
Conclusion of the nuclear radiologist	0.66	0.93	0.61	0.96

*SKFU indicates single-kidney fractional uptake; TTP, time to pyelum; and Tmax time to peak.
†Absolute difference between the kidneys in TTP or Tmax.
‡Renographic curve types 2 represents delayed excretion with preserved washout; curve types 0 and 1, the normal excretion pattern or minor abnormalities, respectively; curve types 3,4 and 5, delayed excretion rate without washout phase, renal failure pattern with measurable kidney uptake, and renal failure without measurable kidney uptake, respectively (adapted from Fommei et al, ref.6).

kidney fractional uptake; with the use of DTPA, there was little difference in the diagnostic accuracy of these parameters. Nevertheless, if the test

result was based on T_{max} and time to pyelum rather than the single-kidney fractional uptake, MAG_3 scintigraphy was still not superior to DTPA scintigraphy.

COMMENT

Study strenghts and limitations

Renal scintigraphy is widely used in the diagnostic work-up of renovascular hypertension. This report summarizes our experience with the technique from 1978 to 1992. During this period, two major modifications were introduced in many clinical centers, including ours (ie, the use of the ACE inhibitor captopril to enhance the difference between the affected and non-affected kidney, and the use of the new radiopharmaceutical ^{99m}Tc-MAG_3, instead of ^{99m}Tc-DTPA).

The numbers of hypertensive patients with and without renal artery stenosis who were included in our analysis of the effect of captopril on the DTPA scan far exceeded those reported in most previously published studies. The European multicenter study by Fommei et al.[6] is the only study that we know of that included a comparable number of patients. To our knowledge, the comparison of MAG_3 scintigraphy with DTPA scintigraphy in our study represents the first systematic within-patient analysis in a substantial number of patients, in contrast to other studies that have been reported to date and that have dealt with only small numbers of patients.[15,21,23] Clinical characteristics of the patients in our study are comparable with those in other studies.[1,5,20]

Because our analysis is retrospective, confounding factors, particularly changes over time in the selection of patients and in the evaluation of renal scans, could not be as well controlled as in a prospective study. This difficulty was in part overcome by (1) studying a large series of consecutive patients in whom both arteriography and scintigraphy were systematically performed, (2) comparing the different scintigraphic procedures in the same patient within a short time interval, and (3) using objective criteria for evaluating the renal scans.

This report addresses the use of renal scintigraphy as a screening

procedure, prior to arteriography, to diagnose the presence of renal artery stenosis. Renal artery stenosis does not equal renovascular hypertension. Essential hypertension is common, and in some patients with renal artery stenosis, the stenosis may not be responsible for the hypertension.

So-called two-kidney one-clip Goldblatt hypertension in animals, which serves as the experimental model of human renovascular hypertension, is generally held to proceed in two, sometimes three, phases.[24] In the early first phase, the rise in blood pressure is largely, if not completely, caused by the rise in circulating renin and angiotensin II. In the second phase, the blood pressure remains high, although the levels of renin and angiotensin II return toward normal. This may be due, at least partly, to the fact that a slightly elevated angiotensin II level, when chronically present, reinforces its own pressor action. In this phase, the secretion of renin from the clipped kidney is still stimulated, and the function of this kidney is highly dependent on angiotensin II. This, in the human equivalent, is illustrated by the increased renal venous renin level on the affected side and the suppressed renin level contralaterally (increased renal vein-renin ratio), by the increased response of peripheral venous renin to the administration of captopril (positive captopril-renin test), and by the effects of this drug on the renal handling of DTPA and MAG_3 (abnormal scan with captopril). In both the first and second phases of two-kidney one-clip Goldblatt hypertension, relief of the stenosis will lead to relief of the hypertension. This is no longer the case in the third and last phase, possibly because of structural changes in the contralateral kidney.

Renovascular hypertension in humans is often defined as being characterized not only by the presence of renal artery stenosis but also by the cure of the hypertension after repair of the stenosis. However, some patients may be in an advanced stage, analogous to the third phase of two-kidney one-clip Goldblatt hypertension, and are therefore not cured by the use of balloon angioplasty or reconstructive surgery. Persistence of the hypertension may also reflect technical failure or recurrence of the stenosis after angioplasty. The most important objection to the use of the blood pressure response to balloon angioplasty or reconstructive surgery as a basis for defining renovascular hypertension is that it is a diagnosis a posteriori and therefore not helpful clinically.

In this report, renal artery stenosis was defined as a reduction of 50% or more of the arterial lumen diameter on the arteriogram. Based on the experimental studies of two-kidney one-clip Goldblatt hypertension, it may be suggested that a more severe stenosis (ie, ≥60% or ≥70%) of the renal artery might be a better definition. However, to our knowledge, this has never been formally tested in clinical studies. Moreover, accurate assessment of the degree of stenosis is difficult in the absence of three-dimensional images, particularly when the lesions are irregular and eccentric.[25] Most important, the radiologist's interpretation of renal arteriograms shows considerable interobserver variability. When experienced radiologists are asked to distinguish among no stenosis, less than 50% stenosis, 50 to 75% stenosis, 76 to 99% stenosis and occlusion, their interpretations of the arteriograms show poor agreement (kappa values, 0.33-0.48).[26] With the use of broader categories (eg, <50% vs ≥50%, or <60% vs ≥60%), the agreement between different radiologists is better, but it is still far from complete.[27,28] In practice, therefore, it is difficult to distinguish between 50% and 60% stenosis with the techniques of arteriography that are routinely used in most hospitals. The 50% stenosis criterion that we used in this report, is also widely used in the literature.[16,25-27,29-32]

This report does not assess the usefulness of renal scintigraphy to predict the outcome of balloon angioplasty or reconstructive surgery. A retrospective study, such as ours, is not suitable for such an assessment, because of the lack of systematic follow-up data on blood pressure after the intervention, the lack of a standardized protocol for antihypertensive drug treatment, and the difficulty to define 'improvement' after intervention.[33]

Effects of captopril on DTPA scintigraphy

The importance of the renin-angiotensin system for maintaining the GFR, when renal perfusion is compromised by artery stenosis, has been demonstrated in animal studies and is also illustrated by clinical observations. The GFR is maintained through angiotensin II-mediated efferent arteriolar constriction. Impairment of renal function after blockade of angiotensin II formation by ACE inhibition has been documented in patients with artery stenosis of a solitary functioning kidney and in bilateral

stenosis. In patients with unilateral stenosis, the percent renal extraction of arterially delivered ^{125}I-labeled thalamate, which is a measure of the filtration fraction, is reduced by captopril, and much more so on the affected than the unaffected side.[18] Captopril also affects the DTPA scintigrams of a kidney with artery stenosis. The renographic curve of such a kidney is characterized by a less steep uptake phase, a later peak, and a flatter downslope in the excretion phase compared with that of the unaffected kidney. These abnormalities are often reinforced by captopril or become manifest after captopril challenge.[1-3]

The single-kidney contribution to the total renal accumulation of DTPA during the uptake phase after injection is commonly used as a diagnostic criterion (single-kidney fractional uptake).[1,5,6,22,34-40] Like other investigators, we observed a decrease in the single-kidney fractional uptake after captopril challenge on the affected side in patients with renal artery stenosis, so that a normal fractional uptake without captopril became abnormal after captopril challenge. However, this was not a uniform finding. In some patients, the single-kidney fractional uptake on the affected side was normal both with and without captopril. Moreover, in some patients with essential hypertension, the normal fractional uptake without captopril became abnormal after captopril challenge. On average, with the single-kidney fractional uptake as the diagnostic criterion, the accuracy of DTPA scintigraphy was not improved by captopril challenge in our series.

Other criteria, T_{max}, time to pyelum, the overall pattern of the renographic curve, and kidney size, appeared to offer no advantages over the single-kidney fractional uptake. In the European multicenter study of the effects of captopril on the DTPA scan, the sensitivity (at a specificity of approximately 0.90) was 0.61 without captopril challenge and 0.70 after captopril challenge with single-kidney fractional uptake as the criterion.[6] For the T_{max}, the sensitivity in that study was only 0.39 without captopril and 0.77 after captopril challenge. The European study also showed that the change in single-kidney fractional uptake caused by captopril challenge was not a more accurate parameter for predicting renal artery stenosis. The findings of our study are in agreement with these results.

MAG_3 vs DTPA

A noteworthy finding in the present study is that the single-kidney fractional uptake on the affected side was higher with MAG_3 than with DTPA in patients with renal artery stenosis, so that the difference in uptake between the affected kidney and contralateral kidney was smaller with MAG_3 than with DTPA. This may be related to the use of captopril in our comparative analysis; MAG_3 is cleared by the kidney mainly by tubular secretion, whereas DTPA is cleared by glomerular filtration. The renal clearance of MAG_3 is a measure of renal blood flow, whereas the renal clearance of DTPA is a measure of glomerular filtration. In the kidney with artery stenosis, captopril has a proportionally larger effect on the GFR than on renal blood flow; in fact, flow may even increase after captopril challenge. These differential effects on filtration and flow are reflected in the decrease in the percent renal extraction of arterially delivered ^{125}I-Thalamate, which equals the filtration fraction.[18] Thus, captopril may cause a greater fall in the single-kidney fractional uptake with DTPA than with MAG_3. We are not aware of any study in which this issue has been systematically addressed. A practical consequence of the smaller difference in uptake between the affected kidney and the contralateral kidney with MAG_3 than with DTPA is the lower accuracy of MAG_3 scintigraphy when the single-kidney fractional uptake is used as a diagnostic criterion.

Like other investigators, we found the T_{max} in MAG_3 scintigraphy to be a better criterion than the single-kidney fractional uptake. However, our results show that the use of this criterion in MAG_3 scintigraphy still did not lead to a higher diagnostic accuracy than could be obtained with DTPA scintigraphy. Our comparison between MAG_3 and DTPA was limited to patients who were studied after captopril challenge. In view of our observations on the effects of captopril on the DTPA scan, it seems unlikely that the diagnostic accuracy with MAG_3 would be superior to that with DTPA in patients who were not challenged with captopril.

Better images are produced with MAG_3 than with DTPA in patients with impaired renal function. According to the Working Party Group on Determining the Radionuclide of Choice,[41] the use of DTPA is not recommended in patients with a serum creatinine greater than 442 μmol/L (>5.0 mg/dL), and DTPA should be used with care if creatinine is greater

than 221 μmol/L (>2.5 mg/dL). The number of such patients in our study was too small to address this point.

Diagnostic value of renal scintigraphy

The prevalence of renal artery stenosis among the general population of hypertensive patients is low, ranging from 1% to 5%.[32] Because renal arteriography is invasive and not without risk, renal scintigraphy has been advocated as a screening procedure to select patients for arteriography. To avoid an unacceptably high number of arteriograms with no abnormalities, the diagnostic specificity of renal scintigraphy must be high. In the present analysis, we chose test results that corresponded with a specificity of 0.90 as cut-off points for a positive test. At this level of specificity, the sensitivity of DTPA scintigraphy ranged from only 0.61 to 0.68, depending on the renographic parameters (ie, single-kidney fractional uptake, T_{max}, time to pyelum, overall shape of renographic curve) that were used. The diagnostic accuracy of MAG_3 scintigraphy with captopril challenge was no better.

Given a test sensitivity of 0.68 and a specificity of 0.90 and assuming a 3% prevalence of renal artery stenosis among the total population of hypertensive patients, then to detect 20 cases in a population of 1000, only 117 subjects need to undergo arteriography if a renal scan with abnormalities is used as a selection criterion for arteriography, whereas 667 subjects will undergo arteriography if scintigraphy is omitted. However, if a renal scan with abnormalities is used as a selection criterion for arteriography, 10 cases of renal artery stenosis will be missed. Obviously, in a population with such a low prevalence, one has little choice but to perform scintigraphy, since it is not practical to perform arteriography in such large numbers of subjects.

Two strategies can be followed as an alternative to scintigraphy. One is the introduction of well-defined and sensible clinical criteria to identify high-risk patients. Practical criteria would need to be strict enough to reduce the number of arteriograms to an acceptable level, but not so rigid as to miss too many cases. The other is the development of less invasive techniques to visualize the renal arteries as a replacement for arteriography (eg, magnetic resonance angiography, spiral computed tomography or duplex ultrasonography). The question of whether much harm is being done by

withholding balloon dilatation or surgical revascularization from a patient who will otherwise need lifelong intensive antihypertensive drug treatment also remains to be answered. Recent reports suggest that a renal scan that shows abnormalities may be associated with a higher chance of a favorable outcome of nonmedical intervention procedures, but it is not certain whether a renal scan that does not show abnormalities is a strong enough reason to refrain from such interventions.[6,34,36,38] A prospective study addressing precisely these issues is now being carried out in the Netherlands.[42] In this multicenter study, strictly controlled standard drug regimens are being used to define refractory hypertension, a standardized protocol for the diagnostic work-up is being followed, and the effects of balloon dilatation and drug therapy are being compared.

Currently, scintigraphy is still the most effective diagnostic procedure to reduce the number of negative arteriograms to a level that is acceptable in terms of burden to the patient and cost. Therefore, when dealing with a population of patients with a low prevalence of renal artery stenosis, it is good policy to perform scintigraphy before deciding to proceed with arteriography. On the other hand, when the prevalence of renal artery stenosis is high, it is reasonable to omit scintigraphy and proceed directly with arteriography. In practice, the omission of renal scintigraphy as a screening step will always result in a substantial number of arteriograms that do not show abnormalities, whereas the use of a renal scan that does show abnormalities as a selection criterion for arteriography will always result in a substantial number of missed diagnoses.

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CHAPTER 3

THE DUTCH RENAL ARTERY STENOSIS INTERVENTION COOPERATIVE (DRASTIC) STUDY: RATIONALE, DESIGN AND INCLUSION DATA

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ABSTRACT

Rationale: Renal artery stenosis may lead to renovascular hypertension, risking multiple organ damage including damage to the contralateral kidney. Progression of stenosis may impair the function of the affected kidney. It is important to identify individuals with this disease among hypertensive patients. The first aim of the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study is to assess the prevalence of renal artery stenosis in patients with well-defined forms of drug-resistant hypertension, and to determine the predictive value of clinical characteristics and diagnostic tests in these pre-selected patients. With regard to treatment, the effect of angioplasty on hypertension is disappointing in atherosclerotic stenosis and technical failure frequently occurs. Therefore, the second aim is to compare the effects of balloon angioplasty and antihypertensive medication on blood pressure in patients with atherosclerotic renal artery stenosis.
Design: Hypertensive patients receiving standard antihypertensive medication in whom diastolic blood pressure remained ≥95 mmHg during three consecutive visits to the outpatient clinic underwent full diagnostic work-up, including renal arteriography. The prevalence of renal artery stenosis in this well-defined patient group was then established, and the predictive value of the various diagnostic tests was assessed. Patients with an atherosclerotic renal artery stenosis of ≥50% were then randomly assigned to balloon angioplasty or to treatment with antihypertensive drugs. After 1 year of intensive follow-up of blood pressure and renal function, re-arteriography was performed.
Conclusion: In total, 1205 patients have been included in the study, about 500 have received diagnostic work-up, and it is expected that 100 patients will be randomly assigned for renal angioplasty or medical treatment.

INTRODUCTION

Obstruction of the renal artery has two important clinical consequences. First, it causes renovascular hypertension with the risk of multiple organ damage. Second, the progressive reduction of blood flow to the kidney leads to impairment of renal function, and eventually to renal insufficiency. On the premise that correction of the stenosis helps to solve these problems, the following issues have to be addressed: since renal artery stenosis is a rare cause of hypertension, how do we detect individuals with this disease among the large population of hypertensive patients? Is treatment of the stenosis effective in lowering the blood pressure and preventing renal insufficiency?

There are many reports describing clinical clues that can predict the presence of renal artery stenosis in a patient with hypertension.[1-6] Most commonly mentioned are: accelerated hypertension, refractory hypertension, abrupt onset of hypertension, hypertension associated with peripheral vascular disease, the presence of an abdominal bruit, and a rise in serum creatinine during treatment with an angiotensin converting enzyme (ACE) inhibitor. Although most of these characteristics are significantly correlated with the presence of renal artery stenosis, they are not very useful in deciding whether or not to perform renal arteriography in a given patient. Most of these characteristics lack a clear definition, and the sensitivity and specificity of each of these characteristics, when used as the criterion to select patients for renal angiography, is much too low. However, when these characteristics are used in combination, one can indeed select a group of patients with a relatively high prevalence of renal artery stenosis (40-50%).[7-12] However, many patients will be missed using this approach.

The limited value of the clinical criteria mentioned above has been the reason for the development of more or less sophisticated functional diagnostic tests. For the moment, renal scintigraphy with radiolabeled diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) or mercaptoacetyltriglycine (^{99m}Tc-MAG$_3$) is the most frequently used test to predict the presence of renal artery stenosis. We investigated the accuracy of baseline and captopril-enhanced scintigraphy performed in consecutive patients (n=225 and n=280 respectively), who underwent renal

arteriography in our clinic in the years 1978-1992 (**Figure 1**). The receiver operating characteristic curves represent the accuracy of DTPA scintigraphy for different cut-off values of single-kidney fractional uptake. When dealing with a relatively rare disease like renal artery stenosis, one has to look for a screening test with high specificity, in the order of 0.90. A test with lower specificity will give too many false-positive results. At a specificity of 0.90, DTPA scintigraphy has a sensitivity of 0.65-0.70. This means that the use of

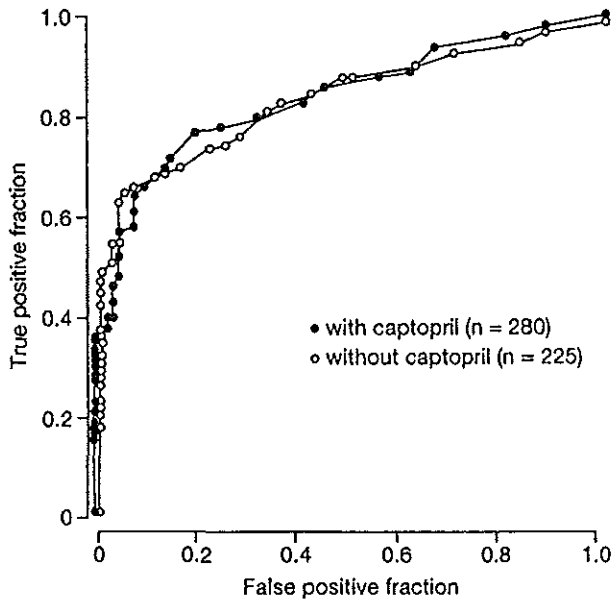

Figure 1. Receiver operating characteristic curves for single-kidney fractional uptake in DTPA scintigraphy with and without captopril challenge. Adapted with permission.[12]

this screening test in a population with a 5% prevalence of renal artery stenosis, will miss about one-third of the patients with renal artery stenosis, while three out of four angiographies will still be negative.

With respect to the treatment of renal artery stenosis, there is general agreement on the benefits of percutaneous transluminal renal angioplasty in patients with fibromuscular dysplasia. In 50% of these patients, the hypertension disappears after angioplasty and a further 42% experience improvement. However, in atherosclerotic renal artery stenosis the success rate is disappointing, because technical failure is not infrequent (about 10%)

and cure is only reached in a minority (about 20%) of technically successful angioplasties.[13] A uniform interpretation of the endpoint "improvement of hypertension" is difficult, because a clear definition is often lacking, so that the interpretation of this endpoint is largely subjective.[13,14]

To address these issues, we designed a study on the diagnosis and treatment of renal artery stenosis. The aim of the study is to answer the following questions: what is the optimal strategy for detecting individuals with renal artery stenosis among the large population of hypertensive patients? Is percutaneous transluminal angioplasty more effective than drug therapy for lowering the blood pressure in patients with an atherosclerotic stenosis? Is it possible to predict the therapeutic effect of angioplasty from the results of functional diagnostic tests? What is a sensible algorithm for the diagnosis and treatment of renal artery stenosis, in light of the cost-effectiveness of angioplasty and the various diagnostic procedures?

DESIGN OF THE STUDY

The study is a multicenter investigation, performed in The Netherlands, with a prospective design. Patients aged between 18 and 75 years who are referred to one of the participating hospitals are recruited (**Figure 2**). The patients are referred for analysis of hypertension, in most cases because the condition is resistant to drug therapy. Secondary hypertension not due to renal artery stenosis is ruled out before inclusion. Other exclusion criteria are: serum creatinine ≥200 μmol/l; unstable coronary artery disease or heart failure; malignant hypertension; and pregnancy. The study is not designed to assess the value of angioplasty in preventing renal insufficiency. Therefore, only patients with relatively normal renal function are included.

At the first visit, information is obtained on contraindications or adverse effects from antihypertensive drugs. When these are not present, the patient is randomly assigned to receive one of two standard drug regimens (**Figure 3**), either 10 mg amlodipine alone or in combination with 50 mg atenolol (Am[+At] regimen), or 20 mg enalapril alone or in combination with 25 mg hydrochlorothiazide (En[+Th] regimen). Combinations of two drugs are given only where patients are older than 40 years of age.

Figure 2. Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study. Location of the participating hospitals in The Netherlands.

Randomization

Age	Drug and dose/day
< 40 years	amlodipine 10 mg
> 40 years	amlodipine 10 mg + atenolol 50 mg

[Am/At regimen]

Age	Drug and dose/day
< 40 years	enalapril 20 mg
> 40 years	enalapril 20 mg + hydrochlorothiazide 25 mg

[En/Th regimen]

Figure 3. The two fixed-dose drug regimens, to which patients without known contraindications or side-effects have been randomly assigned. Am/At, 10 mg amlodipine alone or in combination with 50 mg atenolol; En/Th, 20 mg enalapril alone or in combination with 25 mg hydrochlorothiazide.

Randomization is not possible in patients in whom there is a contraindication or intolerance for the drugs that are used in these two regimens. Such patients are allocated to either the Am(+At) regimen or the En(+Th) regimen, if possible. If this is not possible, the patient is allocated

to a third regimen, which consists of 100 mg atenolol alone or in combination with 25 mg hydrochlorothiazide (At[+Th] regimen). Exceptionally, additional antihypertensive drugs are prescribed. This is the case in patients with severe hypertension, who are treated with three or more drugs at study entry.

Several arguments support the use of these fixed-dose drug regimens. By using such regimens, a clearly defined group of patients with drug-resistant hypertension is selected. This facilitates the evaluation of the results obtained in the therapeutic part of the study. The definition of drug-resistant hypertension, as used in this study, fits in with the accepted practice of proceeding to further diagnostic work-up only when the hypertension is difficult to control. The standard regimens described above are often used in The Netherlands.

In patients treated with an ACE inhibitor, serum creatinine is monitored during treatment to check for a decline in renal function. When this occurs, the patient is allocated to the Am(+At) regimen. In general, when an adverse reaction to the Am(+At) regimen is noted, the patient will be switched to the En(+Th) regimen, and *vice versa*. In the case of adverse reactions or intolerance to both amlodipine and enalapril, the patient switches to the At(+Th) regimen.

INCLUSION DATA

Between January 1993 and September 1996, a total of 43 hospitals were invited to take part in the study. Seventeen centers did not participate: ten centers found the study protocol too time-consuming or estimated a low number of eligible patients in their hospital; one center did not agree with the design of the study; six hospitals that originally agreed to participate did not recruit any patients.

The 26 participating hospitals, six of which were university hospitals, have enrolled 1205 patients (median 15 per hospital). Two-thirds of the patients were enrolled by four centers. At inclusion, there were 72 patients in whom a renal artery stenosis had already been diagnosed by arteriography, before referral to the participating center. These patients went

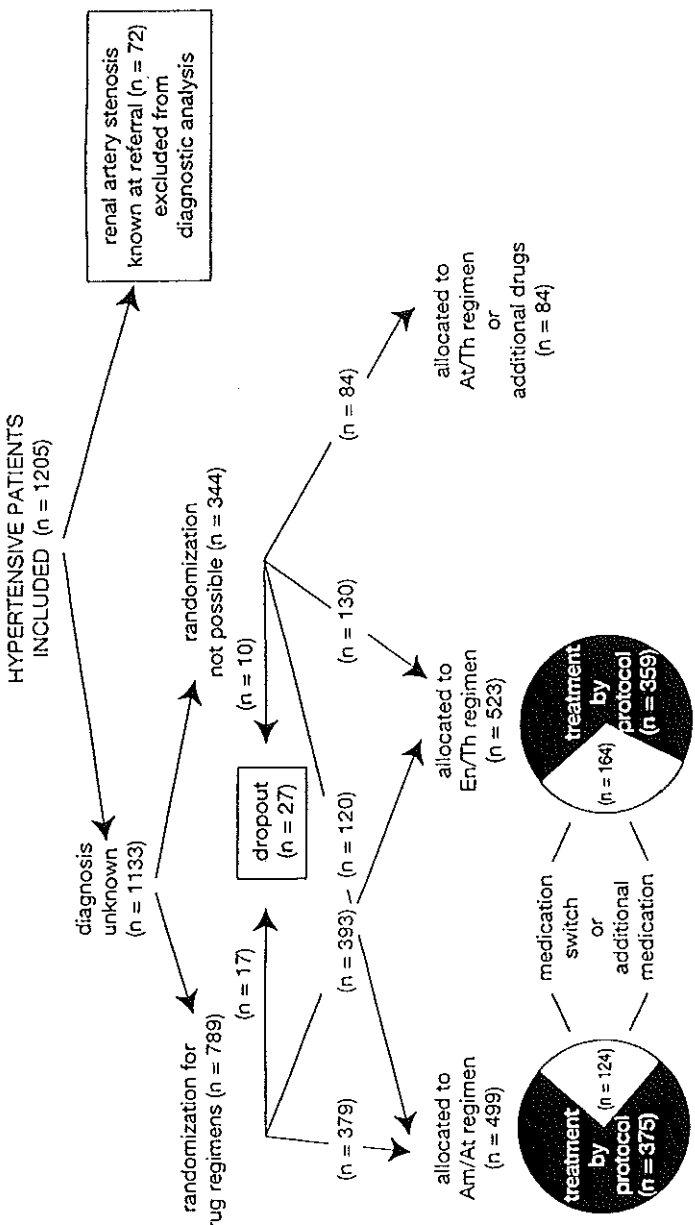

Figure 4. Inclusion data and allocation of patients to the standardized antihypertensive drug regimens. Am/At, 10 mg amlodipine alone or in combination with 50 mg atenolol; En/Th, 20 mg enalapril alone or in combination with 25 mg hydrochlorothiazide; At/Th, 100 mg atenolol or in combination with 25 mg hydrochlorothiazide.

through the diagnostic part of the study to enable their inclusion in the therapeutic part. They will, however, be excluded from the analysis of the diagnostic work-up, in order not to confound the study group with pre-selected patients.

The remaining 1133 patients, in whom the diagnosis was not known, had a blood pressure at inclusion of 179±26/109±12 mmHg, and were taking an average of 1.4±1.1 antihypertensive drugs (mean ± standard deviations). Of these, 789 have been randomly assigned to either the Am(+At) regimen or the En(+Th) regimen, while 344 patients could not be randomly assigned (**Figure 4**). Seventeen of the randomly assigned patients and ten of the patients not randomly assigned did not complete the outpatient study period, and are excluded from further analysis. The final analysis, therefore, includes 379 subjects randomly assigned to the Am(+At) regimen, 393 to the En(+Th) regimen and 334 subjects who were not assigned randomly. Of these non-randomly assigned patients, 120 patients followed the Am(+At) regimen and 130 followed the En(+Th) regimen. Of the remaining patients not randomly assigned, 21 followed the At(+Th) regimen and 63 received other medication. The Am(+At) regimen contained cases that were switched to the En(+Th) regimen and *vice versa*, because of adverse drug reactions. The reason for prescribing other drugs, in addition to the standard regimens, was inadequate blood pressure control by two drugs. The number of patients who were treated exclusively with either Am(+At) or En(+Th) (treatment by protocol) was 375 for the Am(+At) regimen and 359 for the En(+Th) regimen.

CLINIC ATTENDANCE AND DIAGNOSTIC WORK-UP

Patients attend the outpatient clinic at intervals of 1-3 weeks. Blood pressure is measured three times per visit, with the patient in sitting position after a 5 min rest. Measurements are taken according to Riva Rocci using a standard sphygmomanometer, and values are rounded to the nearest 2 mmHg, as recommended by the American Society of Hypertension.[15] All patients receiving the standard drug regimens in whom diastolic blood pressure remains ≥95 are subjected to further diagnostic work-up

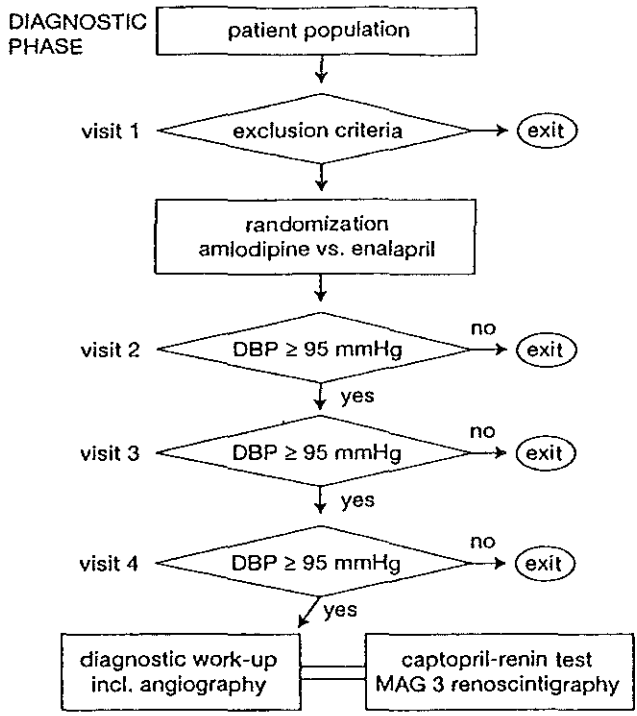

Figure 5. Selection of patients for diagnostic work-up on the basis of hypertension resistant to standardized drug regimens. DBP, diastolic blood pressure; MAG_3, mercapto-acetyltriglycine.

This work-up is also performed in all patients who are treated with more than the standard medication, i.e. more than two drugs or the standard drugs in higher doses, as well as in all patients with a rise in serum creatinine of ≥20 μmol/l during treatment with an ACE inhibitor, irrespective of their blood pressure response. Of the 379 patients who could be evaluated and who were randomly assigned to the Am(+At) regimen, 154 (41%) appeared normotensive at the first ambulant visit, another 65 (17%) at the second and 36 (9%) at the last visit; 124 (33%) patients had drug-resistant hypertension at week 6 and underwent the diagnostic work-up. Because the blood pressure lowering effect of the En(+Th) regimen was somewhat less than that of Am(+At), a larger proportion of patients (181/393; 46%) were

considered to have drug-resistant hypertension or had ACE inhibitor-related impairment of renal function (**Figure 6**).

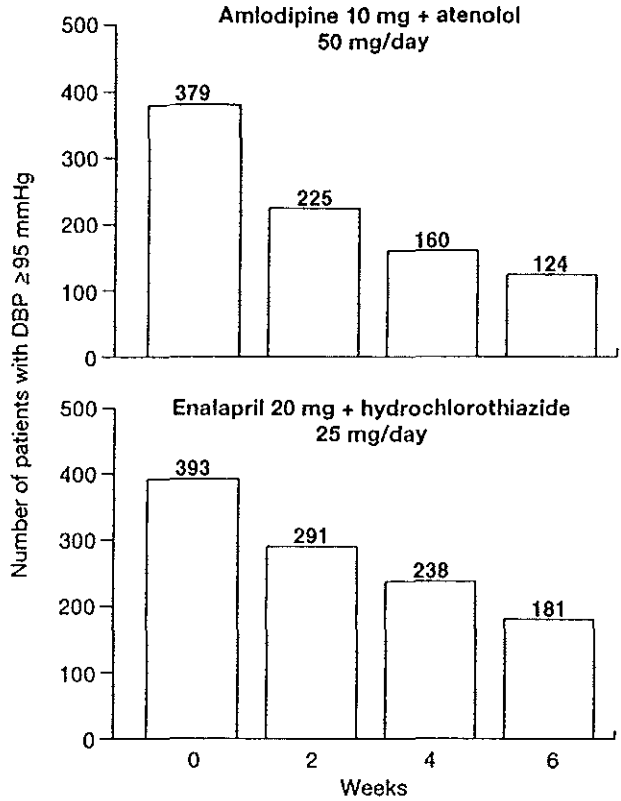

Figure 6. Number of patients, randomly assigned to the standard drug regimens, who were still hypertensive or experienced ACE-inhibitor-related renal function impairment. DBP, diastolic blood pressure.

The diagnostic work-up includes a full medical history, physical examination, laboratory evaluation, the captopril-peripheral renin challenge test,[16] MAG_3 renal scintigraphy after challenge with 50 mg captopril, renal vein renin sampling, a quality-of-life assessment, and in all patients, renal arteriography. Arteriography is performed via the femoral approach, using the digital subtraction technique. The procedure takes place during either a 1-day admittance to the hospital or on an outpatient base, according to local

practice. Radiologists from the participating centers are advised to perform antero-posterior and antero-oblique images (15-30°). Selective arteriography is not required, unless the investigator thinks this necessary. A renal artery stenosis is considered to be present when the arterial luminal diameter is occluded by 50% or more, as judged by the radiologist who performs the arteriography.

The use of an ACE inhibitor may lead to normotension in some patients with renal artery stenosis. When such patients experience no rise in creatinine level, they are overlooked by the study protocol. However, this has not dissuaded the investigators from the use of an ACE inhibitor-containing regimen, because ACE inhibitors are commonly used as first-line antihypertensive therapy. The rationale of the study is not so much to find as many patients with renal artery stenosis as possible, but rather to develop practical and sensible guidelines as to which patients should undergo diagnostic work-up for renal artery stenosis.

THERAPEUTIC PHASE

When the arteriogram reveals a renal artery stenosis, the patient enters the therapeutic part of the study, consisting of a random assignment to renal angioplasty or control medical treatment. Three conditions exclude the patient from this randomization: (1) When the renal artery stenosis is caused by fibromuscular dysplasia, angioplasty is the choice of treatment because of the high success rate of angioplasty in this disease. (2) In case of an atrophic kidney, randomization is not performed, because angioplasty is considered to be unfavorable in such cases. The criterion for an atrophic kidney is a kidney length of less than 8 cm on ultrasound investigation, which is made in all patients with a small kidney size on the arteriogram. (3) When the renal artery is totally obstructed, randomization is not performed because angioplasty is not technically possible.

After randomization, the patients are closely followed for 1 year, with monitoring of blood pressure, drug treatment and serum creatinine. At 3 and 12 months a more extensive evaluation is carried out, consisting of measurement of creatinine and protein in 24-h urine collection, captopril

MAG_3 scintigraphy, and quality-of-life assessment. In addition, re-arteriography is performed in all patients 1 year after the randomization (**Figure 7**).

When the blood pressure is not adequately controlled and the scintigram is still abnormal at the 3-month evaluation in the patients allocated to renal angioplasty (angioplasty failure), the clinician in charge is free to repeat the angioplasty, or proceed to stenting or surgical bypass. Patients allocated to medication who are, by definition, resistant to the standard drug regimens of the diagnostic phase of the study, are treated with three to four antihypertensive drugs according to a step-by-step prescription protocol. When the diastolic blood pressure is ≥95 mmHg at the 3-month evaluation, or when a decline in renal function is observed at any time (defined as a ≥20 μmol/L rise in serum creatinine or a worsening of the MAG_3 scintigram) in these medically treated patients, renal angioplasty is performed. Conversely, when blood pressure is controlled by medical treatment with preservation of renal function, the antihypertensive medication is continued until the end of the study and angioplasty is not performed.

DISCUSSION

This study will provide information on the effectiveness of these two antihypertensive standard drug regimens, and on the prevalence of renal artery stenosis in these patients. The results will also give an insight into the accuracy of some of the most commonly used diagnostic tests. By using these tests and by selecting the most predictive clinical characteristics a "suspicion index" will be developed from which an algorithm can be constructed which will be useful for general practice.

The question of whether the benefits of balloon angioplasty are sufficient to prefer this treatment over medical treatment will hopefully find its answer in the comparison of the 100 or so patients treated with either angioplasty or medical treatment.

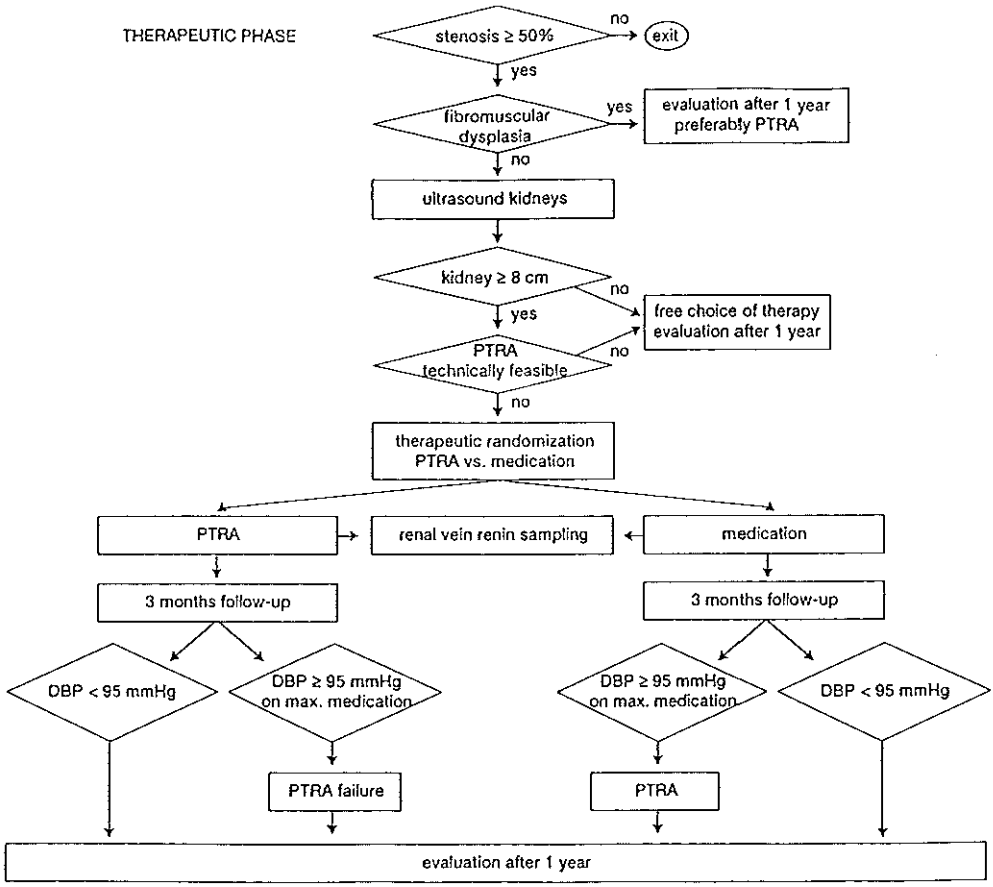

Figure 7. Randomization of patients with atherosclerotic renal artery stenosis for balloon angioplasty or medical treatment, followed by re-arteriography after 1 year. PTRA, percustaneous transluminal renal angioplasty; DBP, diastolic blood pressure.

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CHAPTER 4

RESISTANCE TO ANTIHYPERTENSIVE MEDICATION AS PREDICTOR OF RENAL ARTERY STENOSIS; COMPARISON OF TWO DRUG REGIMENS

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Submitted.

ABSTRACT

Background: Renal artery stenosis is among the most common curable causes of hypertension. The definitive diagnosis is made by renal angiography, an invasive and costly procedure. The prevalence of renal artery stenosis is less than 1% in non-selected hypertensive patients but is higher when hypertension is resistant to drugs.

Objective: To study the usefulness of standardized two-drug regimens for identifying drug-resistant hypertension as a predictor of renal artery stenosis.

Design: Prospective cohort study.

Setting: 26 hospitals in The Netherlands.

Patients: Patients had been referred for analysis of possible secondary hypertension or because hypertension was difficult to treat. Patients ≤40 yr were assigned to either amlodipine 10 mg or enalapril 20 mg, and patients >40 yr to either amlodipine 10 mg combined with atenolol 50 mg or to enalapril 20 mg combined with hydrochlorothiazide 25 mg. Renal angiography was performed (1) if hypertension was drug-resistant, ie, if diastolic pressure remained ≥95 mmHg at 3 visits 1-3 weeks apart or an extra drug was required, and (2) if serum creatinine rose by ≥20 μmol/L (0.23 mg/dL) during ACE inhibitor treatment.

Results: Of the 1106 patients with complete follow-up, 1022 had been assigned to either the amlodipine- or enalapril-based regimens, 772 by randomization. Drug-resistant hypertension, as defined above, was identified in 41% of the patients, and 20% of these had renal artery stenosis. Renal function impairment was observed in 8% of the patients on ACE inhibitor, and this was associated with a 46% prevalence of renal artery stenosis. In the randomized patients, the prevalence of renal artery stenosis did not differ between the amlodipine- and enalapril-based regimens.

Conclusions: In the diagnostic work-up for renovascular hypertension the use of standardized medication regimens of maximally 2 drugs, to identify patients with drug-resistant hypertension, is a rational first step to increase the a priori chance of renal artery stenosis. Amlodipine- or enalapril-based regimens are equally effective for this purpose.

INTRODUCTION

Renal artery stenosis is among the most common curable causes of hypertension, but its prevalence in non-selected patient populations is less than 1%.[1] The definitive diagnosis is made by renal angiography, an invasive procedure that is costly and not without risk. The question of how to select hypertensive subjects for angiography is therefore of considerable interest.

While the diagnosis of renal artery stenosis as an anatomical lesion is not without difficulties, the assessment of its functional significance is even more problematic. The effects of captopril or other angiotensin converting enzyme (ACE) inhibitors on the renal scintigram, and measurements of renal vein renin have been used to predict angioplastic outcome. The predictive power of these tests is at best dubious,[2-7] and renal vein renin sampling is a complex procedure. Rather than pursuing ever more sophisticated diagnostic procedures in an effort to find as many cases as possible, a better strategy could be to restrict diagnostic work-up to patients in whom hypertension is difficult to control by medication. The prevalence of renal artery stenosis is relatively high in such patients,[8-11] and they are also the patients who may benefit most from angioplasty. There is, however, no uniform definition of so-called drug-resistant hypertension, because of the wide variety of antihypertensive drugs and drug regimens.

Renal artery stenosis is often associated with some degree of renin-angiotensin system hyperactivity, and ACE inhibitor treatment has been reported to be particularly effective in lowering blood pressure in patients with increased renin.[12] Persistent hypertension despite ACE inhibitor treatment, may therefore argue against the presence of renal artery stenosis. On the other hand, in some patients with renal artery stenosis renal function is highly angiotensin II-dependent,[13,14] so that the occurrence of renal function impairment during ACE inhibitor treatment may help to identify these patients.

The objective of our study is to investigate the usefulness of standardized drug regimens for the identification of drug-resistant hypertension as a predictor of renal artery stenosis; a regimen consisting of amlodipine and atenolol was compared with a regimen consisting of enalapril and

hydrochlorothiazide, both regimens being frequently used in first-line antihypertensive therapy. This report is part of the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study.

METHODS

The DRASTIC study is a prospective study on renovascular hypertension, conducted at 26 clinical centers in the Netherlands. The aims were (1) to design a strategy for selecting hypertensive patients for further diagnostic work-up and to optimize this work-up, and (2) to compare the effects of percutaneous transluminal renal angioplasty on blood pressure and renal function with the effects of drug treatment. The present paper focuses on the question of how to select patients for diagnostic work-up. The protocol for this study was approved by the ethics committees of the participating hospitals. All patients gave written informed consent.

Patient selection

The study was carried out in hypertensive patients aged 18-75 yr, who had been referred to the participating centers from January 1993 to September 1996. Reasons for referral were unsatisfactory blood pressure control or an adverse drug effect during the course of antihypertensive treatment, or analysis of possible secondary hypertension. Exclusion criteria were: suspected secondary hypertension other than renovascular disease, unstable coronary artery disease, heart failure, renal failure (serum creatinine ≥200 μmol/L, [2.26 mg/dL]), and inadequate contraception. Secondary hypertension other than renovascular disease was specified as abnormal urinalysis, signs of obstructive uropathy or renal scarring, symptoms or signs of pheochromocytoma or Cushing syndrome, or hypokalemia associated with low plasma renin.

Standardized drug regimens

At intake, a record was made of the antihypertensive drugs the patient had been using. This medication was discontinued and the patient was

assigned to one of the standardized drug regimens, which consisted of the calcium antagonist amlodipine (Am), the ACE inhibitor enalapril (En), the beta-blocker atenolol (At) and the diuretic hydrochlorothiazide (Th) in various combinations (**Table 1**). Patients ≤40 yr were randomly assigned to either Am or En treatment, while patients >40 yr were assigned to either Am+At or En+Th.

Table 1. Standardized antihypertensive drug regimens.

	Patients ≤40 yr		Patients >40 yr	
Regimens	Drugs	DDDs*	Drugs	DDDs*
Am(+At)	Amlodipine 10 mg once daily	2.00	Amlodipine 10 mg once daily + Atenolol 50 mg once daily	2.67
En(+Th)	Enalapril 20 mg once daily	2.00	Enalapril 20 mg once daily + Hydrochlorothiazide 25 mg once daily	3.00
At(+Th)	Atenolol 100 mg once daily	1.33	Atenolol 100 mg once daily + Hydrochlorothiazide 25 mg once daily	2.33

*Total number of defined daily doses (DDD; the DDD is the assumed average maintenance dose per day for a drug used on its main indication in adults).[18]

Patients who could not be treated with Am(+At) because of previous adverse reactions or (relative) contra-indications were treated with the En(+Th) regimen and *vice versa*. Patients who could not be treated with either Am or En received the At (+Th) regimen. Relative contra-indications were serum creatinine >120 μmol/L (1.36 mg/dL) in the case of En and Th, chronic obstructive pulmonary disease or intermittent claudication in the case of At, and diabetes mellitus in the case of At and Th. Relative indications for the use of At were angina pectoris or palpitations. When adverse reactions occurred during one of the standardized medication protocols, the patient switched to the other protocol. Drugs other than Am, En, At or Th were used in patients who could not be assigned to any of the standardized regimens because of multiple adverse reactions or because

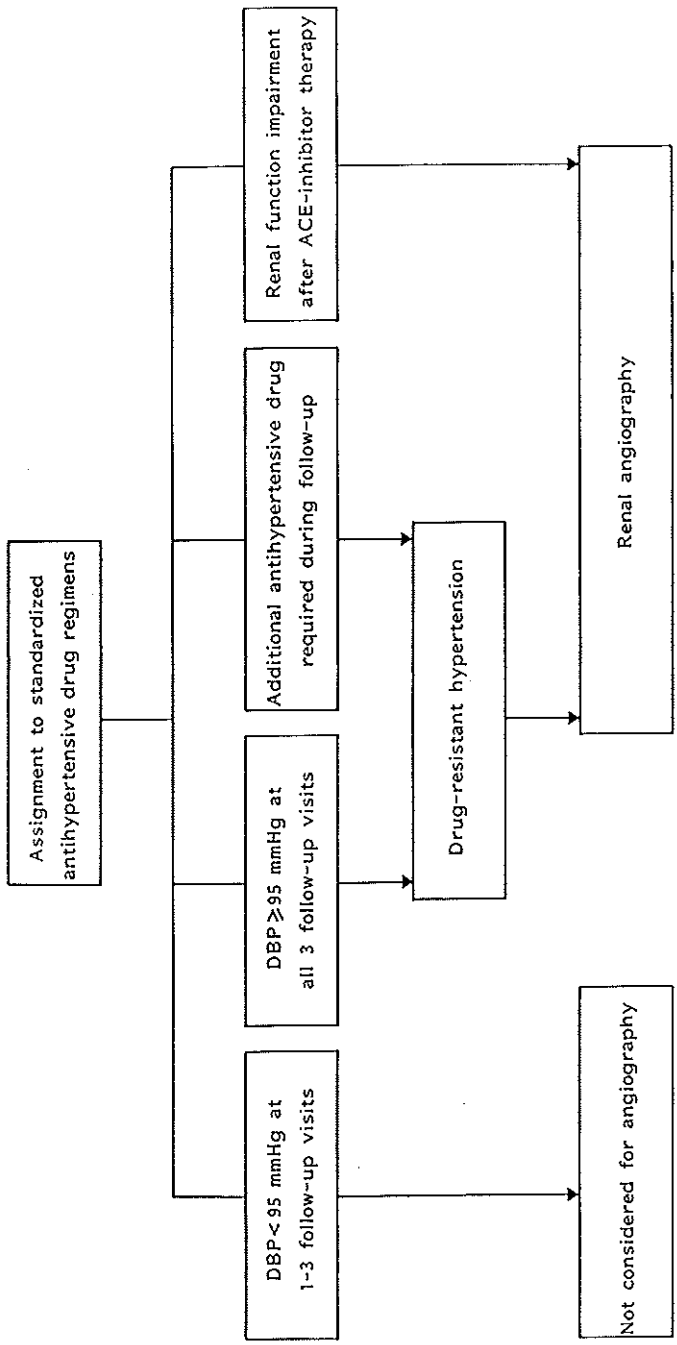

Figure 1. Study design.

their hypertension was considered too severe to be treated with only two drugs.

Follow-up and renal angiography

After intake, patients were seen at 3 consecutive visits, 1-3 weeks apart. Blood pressure was measured by standard sphygmomanometry, with the patient in the sitting position after 5 minutes of rest.[15] Measurements were made in triplicate and the results were averaged. During treatment with En(+Th), serum creatinine was monitored.

Patients who remained hypertensive, ie, diastolic blood pressure ≥95 mmHg during all three follow-up visits while on standardized medication, as well as patients requiring the addition of an extra drug during follow-up, were identified as having drug-resistant hypertension (**Figure 1**). Patients who could not be assigned to any of the standardized regimens and who required more than 2 drugs (or more than 1 drug when ≤40 yr), were also considered to have drug-resistant hypertension. All patients with drug-resistant hypertension were requested to undergo renal angiography. Angiography was also performed in the patients who showed a ≥20 μmol/L (0.23 mg/dL) rise in serum creatinine during treatment with an ACE inhibitor, irrespective of their blood pressure response.

Angiography was carried out intra-arterially, using the digital subtraction technique. Radiologists from the participating centers were advised to make antero-posterior and antero-oblique (15-30 degrees) images; selective angiography was not routinely performed. The interpretation of the angiograms was carried out by the radiologist who had performed the investigation. Renal artery stenosis was defined as a reduction of the arterial lumen diameter by 50% or more.

Statistical analysis

Comparisons were made by the Student's *t* test or the Wilcoxon rank sum test. For comparing the proportions of patients between groups, the Chi square test was used. All calculations of *P* values were two-tailed. The patients who could not be randomly assigned to the standardized drug regimens, were analyzed separately from the randomized patients, because

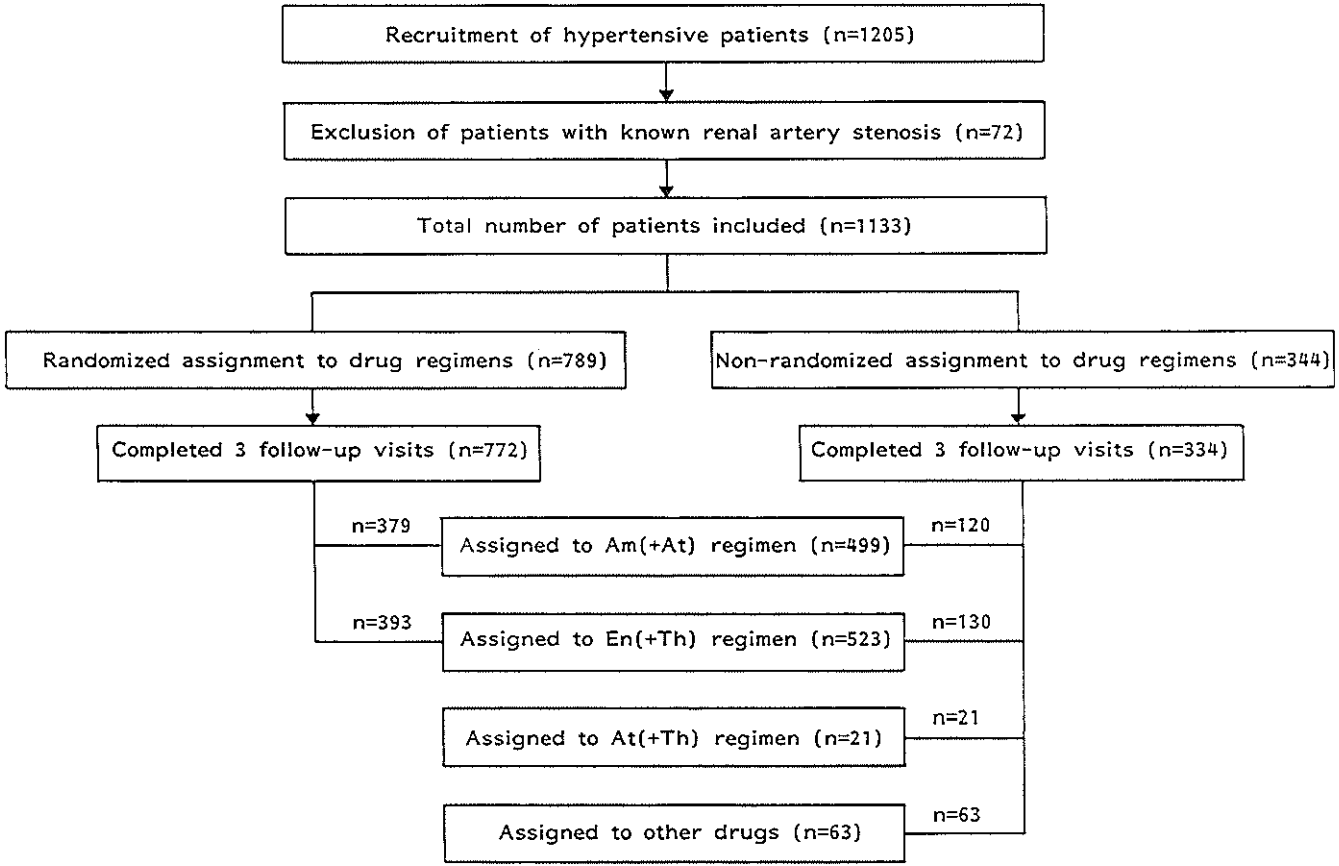

Figure 2. Numbers of patients assigned to the standardized drug regimens.

the prevalence of drug-resistant hypertension is likely to be related to some of the reasons for non-randomization.

RESULTS

Assignment to standardized drug regimens

Enrolled in the study were 1205 patients. In 72 of them, a scintigraphic and/or angiographic diagnosis of renal artery stenosis had been made before assignment to standardized drug treatment. These patients were therefore excluded. The remaining 1133 patients (51.2±12.4 yr, mean±SD) were using an average of 1.4±1.1 antihypertensive drugs at entry, in a dose corresponding with 2.0±1.9 defined daily doses (DDDs; one DDD is the assumed average maintenance dose per day for a drug used on its main indication in adults).[16] Blood pressure at entry was 179±26 mmHg systolic and 109±12 mmHg diastolic. Serum creatinine was 86 (40-199) μmol/L (median, range). The large majority of patients was assigned to either Am(+At) or En(+Th), three-quarters of them by randomization (**Figure 2**). The reasons for non-randomization are given in **Table 2**. Of the 499 patients with complete follow-up who started with Am(+At), 375 patients used only Am(+At) for the full period of follow-up, 17 received an additional drug, and 107 were switched to a different regimen. Of the 523 patients with complete follow-up who started with En(+Th), 359 patients remained on this regimen, 21 received an additional drug, and 143 were switched to a different regimen.

Follow-up

Complete blood pressure data were available in 1106 patients. Although these patients were referred to the participating centers because of difficult-to-treat hypertension, a large proportion became normotensive during follow-up while on the standardized treatment regimens with one or two drugs. Drug-resistant hypertension, as defined by the criteria of the present study, was demonstrated in 455 patients (41%). Of these patients, 92 (20.2%) were ≤40 yr. Blood pressure at entry was higher among

Table 2. Contra-indications, relative contra-indications and indications that precluded randomized assignment to standardized drug regimens.

Randomized assignment to En(+Th) not possible; assignment to Am(+At) (n=120)

Reason	Number of patients
cough	39
allergic symptoms	8
gastro-intestinal complaints	4
impaired renal function*	16
gout	11
angina pectoris, palpitations	17
other or not recorded	25

Randomized assignment to Am(+At) not possible; assignment to En(+Th) (n=130)

Reason	Number of patients
edema	15
flushes/headache	10
impotence	3
cold acra	3
bradycardia	7
allergic symptoms	5
intermittent claudication	15
chronic obstructive pulmonary disease	33
diabetes mellitus	3
mild heart failure	6
other or not recorded	30

Randomized assignment containing En or Am not possible; assignment to At(+Th) (n=21)

Reason	Number of patients
angina pectoris	6
impaired renal function*	2
cough	1
combinations of above	6
other or not recorded	6

Assignment to other drug combinations (n=63)

Reason	Number of patients
angina pectoris	4
impaired renal function*	5
cough	2
gout	1
headache	2
combinations of above	18
other or not recorded	31

*Serum creatinine ≥120 µmol/L (1.36 mg/dL).

drug-resistant patients, and they used more medication (**Table 3**). In the drug-resistant group, blood pressure during follow-up was 170±22 mmHg systolic and 105±9 mmHg diastolic (average of the 3 follow-up visits) while on 3.2±1.1 DDDs of antihypertensive drugs. Of the patients with complete follow-up, 43 of the 523 starting on ACE inhibitor (8%) showed a rise in serum creatinine by ≥20 μmol/L (0.23 mg/dL). Creatinine at entry was higher in these patients than in those with stable creatinine levels (98, 59-199 μmol/L vs 83, 40-197 μmol/L (1.11, 0.67-2.25 mg/dL vs 0.94, 0.45-2.23 mg/dL), median and range, P=0.002).

Table 3. Inclusion characteristics of patients who became normotensive on standardized drug treatment compared to patients who remained hypertensive.

	Patients who became normotensive n=608	Patients who remained hypertensive n=455	*P*
Systolic blood pressure at entry (mmHg)	174±25	185±26	<0.001
Diastolic blood pressure at entry (mmHg)	106±11	112±12	<0.001
Defined daily doses of drugs used at entry	1.4±1.6	2.7±2.1	<0.001
Age (yr)*	50.7±12.4	51.8±12.4	0.14
Sex (% male)	45.1%	56.4%	<0.001
Serum creatinine at entry (μmol/L)	86.1±20.6	92.7±24.9	<0.001
Patients referred by general practitioner (%)	61.8 (%)	54.2 (%)	0.01

*Of the patients who became normotensive 123 (18%) were ≤40 yr, of the patients who remained hypertensive 92 (20%) were ≤40 yr.

Table 4 gives the prevalence of drug-resistant hypertension and the incidence of renal function impairment after ACE inhibitor treatment in the groups randomly assigned to Am(+At) or En(+Th) and in the groups not randomly assigned to these and other regimens. In the randomized patients, a larger proportion remained hypertensive during En(+Th) treatment than during Am(+At) treatment. The prevalence of drug-resistant hypertension was higher in the combined non-randomized groups than in the combined randomized groups (51 vs 37%, P<0.001). The non-randomized groups also

Table 4. Prevalence of persistent hypertension and incidence of ACE inhibitor-related renal function impairment during standardized drug treatment. Prevalence of renal artery stenosis in patients with persistent hypertension or ACE inhibitor-related renal function impairment who underwent angiography.

	Randomized assignment to		Non-randomized assignment to		
Number of patients with:	Am (+At) regimen n=379	En (+Th) regimen n=393	Am (+At) or En (+Th) regimen n=250	Other drug regimens n=84	Total n=1106
Persistent hypertension (n, %)	122 (32%)	164 (42%)*	104 (41%)	65 (77%)	455 (41%)
Refused angiography (n)	4	5	6	1	16
Underwent angiography (n)	118	159	98	64	439
Renal artery stenosis (n, %)	20 (17%)	17 (11%)	23 (23%)	29 (45%)	89 (20%)
ACE inhibitor-related renal function impairment (n, %)	2 (0.5%)†	17 (4%)	22 (9%)	2 (2%)	43
Refused angiography (n)	0	2	2	0	4
Underwent angiography (n)	2	15	20	2	39
Renal artery stenosis (n, %)	0 (0%)	6 (40%)	10 (50%)	2 (100%)	18 (46%)

*P=0.006 for difference with Am(+At) regimen.
†These patients were switched to the En(+Th) regimen because of an adverse reaction to the Am(+At) regimen.

showed a higher incidence of renal function impairment after ACE inhibitor treatment (7 vs 2%, $P<0.001$).

Renal angiography

Renal angiography was performed in 478 patients. The overall prevalence of renal artery stenosis was 22%. The stenosis was caused by atherosclerosis in 87 patients (81%) and by fibromuscular dysplasia in 17 (16%); distinction between these two causes was unclear in 3 patients. Fibromuscular dysplasia was observed in 75% of stenoses in patients ≤40 yr, and in 11% in patients >40 yr ($P<0.001$). Complications of angiography were groin hematoma necessitating blood transfusion (n=5), vasovagal syncope (n=2), and occlusion of the femoral artery, which had to be treated by surgical thrombectomy (n=1).

Table 4 shows the prevalence of renal artery stenosis in the patients who had drug-resistant hypertension or experienced ACE inhibitor-related renal function impairment in the different drug treatment groups. The prevalence of renal artery stenosis among the patients who underwent angiography was higher in the combined non-randomized groups than in the combined randomized groups (35 vs 15%, $P<0.001$). In the randomized patients, the overall prevalence of renal artery stenosis was not different between the Am(+At) and En(+Th) groups (17 vs 13%, $P=0.41$). The prevalence among patients ≤40 yr was lower than among patients >40 yr (10 vs 25%, $P=0.002$). Bilateral stenosis was present in 20 patients (23%) with renal artery stenosis in the drug-resistant group and in 7 (39%) in the renal function impairment group ($P=0.15$). The prevalence of risk factors for renal artery stenosis in the different medication groups is given in **Table 5**. Older age, vascular occlusive disease, smoking history and elevated serum creatinine were more common in the non-randomized patients.

DISCUSSION

Renovascular hypertension is defined as hypertension caused by renal artery stenosis. Restoration of blood pressure after repair of the stenosis is therefore the diagnostic proof. This, however, is a diagnosis a posteriori and

Table 5. Risk factors for renal artery stenosis in the patients who underwent renal angiography.

	Angiography after randomized assignment to		Angiography after non-randomized assignment to		
	Am (+At) regimen n=120	En (+Th) regimen n=174	Am (+At) or En (+Th) regimen n=118	Other drug regimens n=66	*P**
Age (yr)	48.5±12.6	49.8±12.1	55.2±11.2	56.3±11.4	<0.001
Sex (% male)	50.0%	59.8%	56.8%	56.1%	0.43
History or signs of vascular occlusive disease (%)†	21.4%	30.4%	45.6%	58.7%	<0.001
Smoking >10 yr (%)	48.7%	62.7%	66.9%	75.4%	<0.001
Body mass index (kg/m²)	27.0±5.0	27.1±4.9	26.4±4.2	26.2±3.8	0.42
Hypertensive retinopathy grade III or IV (%)	23.3%	21.2%	18.3%	18.9%	0.90
Abdominal bruit (%)	5.9%	7.7%	11.4%	14.5%	0.19
Serum creatinine (μmol/L)	89±21	90±24	101±31	103±34	<0.001
Hypercholesterolemia (%)‡	31.0%	28.5%	33.3%	57.1%	0.22

*Statistical comparison was made for 4 groups.
†Cerebrovascular accident, myocardial infarction, vascular surgery, angina pectoris, intermittent claudication, carotid or femoral bruit.
‡Serum cholesterol ≥6.5 mmol/L (251.4 mg/dL) or cholesterol-lowering therapy.

therefore of little practical value. Moreover, hypertension may persist after angioplasty due to technical failure of the procedure or restenosis. It is also possible that the patient has entered the advanced stage of hypertension, which corresponds with the irreversible phase of Goldblatt hypertension in animals.[17] The present paper describes a prospective cohort study and addresses the question of how to select patients for diagnostic work-up for renovascular hypertension. The outcome after balloon angioplasty will be reported in a separate paper.

In the clinical context, the demonstration of renal artery stenosis is a key step in the diagnosis of renovascular hypertension. Most clinicians agree that diagnostic work-up, including renal angiography, is warranted in patients who do not respond satisfactorily to so-called triple therapy.[9] On the other hand, few clinicians will advise adult patients, even those under 40 years, to undergo angiography when blood pressure can be readily controlled with one drug. Our study was primarily aimed at patients who belong to the intermediate category, ie, patients >40 yr who remain hypertensive despite treatment with two drugs, and patients ≤40 yr who remain hypertensive while on treatment with one drug. The choice of 40 years of age as the point where a different strategy may apply, is arbitrary. It arises from the intention not to miss fibromuscular dysplasia, which has a higher prevalence at younger age and can be treated successfully by balloon angioplasty with less risk of restenosis than in atherosclerotic disease.[18]

The treatment regimens in this study are frequently used in The Netherlands. The drugs in these regimens belong to classes that are also used in other countries, although individual drugs and dosages may differ between countries. It is probably justifiable to extrapolate our results to other drug regimens, provided that these regimens are of comparable antihypertensive efficacy. The number of DDDs may be used as a measure of comparison. The standardized Am(+At) and En(+Th) medications in our study correspond with 2(+0.67) and 2(+1) DDDs respectively.

Selection criteria for renal angiography in our study were drug-resistant hypertension or ACE inhibition-related renal function impairment. We found that persistent hypertension was more common in the patients randomized to the En (+Th) protocol than in the patients randomized to the

Am (+At) protocol. The prevalence of renal artery stenosis in the patients who had persistent hypertension and were subjected to angiography was, however, not different between the two groups. In the patients randomized to En(+Th), deterioration of renal function following administration of the ACE inhibitor was rare, so that this effect had little diagnostic impact, despite the high prevalence of renal artery stenosis in patients showing this phenomenon. Deterioration of renal function after ACE inhibition was not an exclusive finding for patients with bilateral disease, in fact, more than half of the patients with this finding had unilateral renal artery stenosis. Probably concurrent arteriolosclerosis is responsible for the decrease in glomerular filtration after eliminating the effect of angiotensin II.

We did not investigate the prevalence of renal artery stenosis in the patients who showed adequate blood pressure control after medical treatment. Literature data suggest that in these patients renal artery stenosis is rare, because refractory hypertension is a powerful predictor of renal artery stenosis.[10,19] Moreover, identification of renal artery stenosis when the hypertension can be readily controlled by drugs is of less practical importance, because such patients have a smaller chance to develop target organ damage. Since blood pressure in patients with renal artery stenosis is said to be particularly responsive to ACE inhibition, one could argue that we missed more cases in the group randomized for En(+Th) than in the group randomized for Am(+At). This seems unlikely, because our detection rate in the En(+Th) group was not lower than in the Am(+At) group, while in both groups 96% of the patients eligible for angiography had indeed been subjected to this procedure.

The non-randomized patients had a higher prevalence of renal artery stenosis than the randomized patients. This is to be expected, given the fact that the reasons for non-randomization included the presence of angina pectoris or claudication, which are symptoms of atherosclerotic disease. Elevated serum creatinine was also a reason for non-randomization, and this can be a sign of atherosclerotic disease of the renal arteries or smaller renal vessels.

In a previous paper we reported on a simple clinical rule to predict renal artery stenosis in hypertensive patients. This rule was designed on the basis of the DRASTIC database, and was found to apply to patients in whom the

hypertension was resistant to En(+Th) as well as to patients resistant to Am(+At).[20] It takes into account a number of risk factors, such as age, smoking history and the serum levels of cholesterol and creatinine, and appeared to be reliable in a retrospective design to discriminate between patients with and without renal artery stenosis.

We conclude that the use of standardized two-drug regimens to identify drug-resistant hypertension, is sufficient to increase the average a priori chance of renal artery stenosis to 10% or more. In this respect, the combination amlodipine (10 mg) and atenolol (50 mg) appears to be as effective as the combination enalapril (20 mg) and hydrochlorothiazide (25 mg). ACE inhibition-related renal function impairment is too rare to make the enalapril/thiazide combination a better predictor of renal artery stenosis than the amlodipine/atenolol combination. The use of these two-drug combinations is a rational first step in the diagnostic work-up for renovascular hypertension. By taking into consideration some other well known clinical characteristics, the risk estimation can be narrowed down to the individual patient.

APPENDIX

In addition to the authors, the members of the Dutch Renal Artery Stenosis Intervention Cooperative Study Group include the following investigators and institutions, listed in descending order of the number of patients enrolled: F.M.E. Hoekstra, A.H. van den Meiracker (University Hospital Rotterdam, Rotterdam); A.K.M. Bartelink, S.J. Eelkman Rooda and C.A.M.J. Gaillard (Eemland Hospital, Amersfoort); A. Dees (Ikazia Hospital, Rotterdam); J.W.M. Lenders and Th. Thien (University Hospital St. Radboud, Nijmegen); J.A.C.A. van Geelen (Medical Center, Alkmaar); C.J. Doorenbos (Deventer Hospitals, Deventer); J. van der Meulen and P Smak Gregoor (Merwede Hospital, Dordrecht); P.W. de Leeuw, P.N. van Es, M.M.E. Krekels and A.A. Kroon (University Hospital Maastricht, Maastricht); F. van Berkum and R. Lieverse (Ruwaard van Putten Hospital, Spijkenisse); P. Chang, A .Cohen and A.A.M.J. Hollander (Department of Nephrology, University Hospital Leiden, Leiden); G. Schrijver (Rode Kruis Hospital, Beverwijk); P.J. Wismans (Havenziekenhuis, Rotterdam); F. de Heer, F.L.G. Erdkamp (Maasland Hospital, Sittard); R.M. Brouwer and W.A.H. Koning (Medisch Spectrum Twente, Enschede); P.P.N.M. Diderich (St. Franciscus Gasthuis, Rotterdam); G.A. van Montfrans (University Medical Center, Amsterdam); W. Hart (Reinier de Graaf Gasthuis, Delft); E.J. Buurke (Westeinde Hospital, Den Haag); J.H. Bolk (Department of Internal Medicine, University Hospital Leiden, Leiden); H.H. Vincent (St. Antonius Hospital, Nieuwegein); F.L Waltman (Oosterschelde Hospital, Goes); T.L.J.M. van der Loos and F.J.M. Klessens-Godfroy (Oogziekenhuis, Rotterdam); G. Kolsters (Hospital De Weezenlanden, Zwolle); J. Silberbusch and K.J. Parlevliet (Onze Lieve Vrouwe Gasthuis, Amsterdam); S, Lobatto (Hospital Hilversum).

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CHAPTER 5

A CLINICAL PREDICTION RULE FOR RENAL ARTERY STENOSIS

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ABSTRACT

Background: Renal artery stenosis is a rare cause of hypertension. The gold standard for diagnosing renal artery stenosis, renal angiography, is invasive and costly.

Objective: To develop a prediction rule for renal artery stenosis from clinical characteristics that can be used to select patients for renal angiography.

Design: Logistic regression analysis of data from a prospective cohort of patients suspected of having renal artery stenosis. A prediction rule was derived from the regression model for use in clinical practice.

Setting: 26 hypertension clinics in The Netherlands.

Patients: 477 hypertensive patients who underwent renal angiography because they had drug-resistant hypertension or an increase in serum creatinine concentration during therapy with angiotensin-converting enzyme inhibitors.

Results: Age, sex, atherosclerotic vascular disease, recent onset of hypertension, smoking history, body mass index, presence of an abdominal bruit, serum creatinine concentration and serum cholesterol level were selected as predictors. The regression model was reliable (goodness-of-fit test, $P>0.2$), and discriminated well between patients with stenosis and those with essential hypertension (area under the receiver-operating characteristic curve, 0.84). The diagnostic accuracy of the regression model was similar to that of renal scintigraphy, which had a sensitivity of 72% and specificity of 90%.

Conclusions: In the diagnostic work-up of patients suspected of having renal artery stenosis, the clinical prediction rule can be considered as an alternative to renal scintigraphy. It can help to select patients for renal angiography in an efficient manner by reducing the number of angiographic procedures without the risk for missing many renal artery stenoses.

INTRODUCTION

Renal artery stenosis impairs blood flow to the kidney and can consequently cause renovascular hypertension and renal failure.[1,2] Although the prevalence of this condition among patients with hypertension is low, therapeutic options for relieving renal artery stenosis, such as renal angioplasty and stenting, make the search for renal artery stenosis worthwhile.[2-4] Renal angiography is the gold standard for diagnosing renal artery stenosis, but it is a costly and invasive procedure that can involve serious complications.[5,6]

To diagnose renal artery stenosis efficiently, angiography should be used selectively. Most physicians rely on captopril renal scintigraphy as a selection criterion, but the diagnostic accuracy of this test is low (sensitivity, 65% to 77%; specificity, 90%.[7,8] As an alternative, clinical characteristics can be used to select hypertensive patients for angiography.[9] Patients with normal renal function whose blood pressure can be controlled with one or two drugs can be excluded from angiography.[9,10] In the remaining patients (those with drug-resistant hypertension), such clinical characteristics as atherosclerotic vascular disease, smoking history, and presence of an abdominal bruit can be used to estimate a patient's probability of renal artery stenosis.[11-14] This estimate can then be used in selection for angiography.

We analyzed the clinical characteristics of 477 patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with angiotensin-converting enzyme (ACE) inhibitors who participated in the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study.[9] We developed a clinical prediction rule for quantifying the probability of renal artery stenosis[15] and demonstrated the potential consequences of this rule for clinical practice by applying it to our patients.

PATIENTS AND METHODS

Patients

The DRASTIC study is a prospective cohort study conducted at 26 departments of internal medicine with an interest in hypertension throughout The Netherlands.[9] The diagnostic phase of the study was designed to find an optimal strategy for diagnosing renal artery stenosis. In the DRASTIC study, 1133 hypertensive patients 18 to 75 years of age with preserved renal function serum creatinine ≤200 μmol/L [2.26 mg/dL]) were enrolled. These patients were referred for analysis of hypertension by general practitioners (55%) or hospital specialists (45%), in most cases because their hypertension was difficult to treat with antihypertensive drugs. Sixty percent of patients were from four hospitals. After giving written informed consent, patients were randomly assigned to one of two standard protocols with antihypertensive drugs: amlodipine, 10 mg, plus atenolol, 50 mg, in patients older than 40 years of age, or enalapril, 20 mg, plus hydrochlorothiazide, 25 mg, in patients older than 40 years of age. Blood pressure was measured with a standard sphygmomanometer at three consecutive visits at least 1 week apart. Measurements were taken three times per visit after a 5-minute rest with the patient in the sitting position. Patients were selected for diagnostic work up if they had drug-resistant hypertension, defined as a mean diastolic blood pressure per visit of 95 mmHg or more while receiving the standard drug regimen during all three visits or prescription of an additional drug regardless of the blood pressure response. Patients were also selected if the serum creatinine concentration increased 20 μmol/L (0.23 mg/dL) or more during therapy with ACE inhibitors. In these patients, intra-arterial digital subtraction angiography and other, noninvasive tests were performed. In accordance with the study protocol, patients who responded well to standard treatment were not evaluated further. The diagnostic phase of the study was followed by a therapeutic phase in which patients with atherosclerotic stenosis were randomly assigned to receive medication or renal angioplasty.

Definitions

After performing a literature study, we selected 12 clinical characteristics indicative of renovascular disease (predictors):[10,11,16-26] age, sex, ethnicity (black or other), signs and symptoms of atherosclerotic vascular disease (femoral or carotid bruit, angina pectoris, claudication, myocardial infarction, cerebrovascular accident, or vascular surgery), recent onset of hypertension (within the past 2 years), family history of hypertension (parents, siblings, or children with hypertension), smoking history (ever or never), obesity (body mass index ≥25 kg/m^2), abdominal bruit, advanced hypertensive retinopathy (fundus grade III or IV), serum creatinine concentration, and hypercholesterolemia (serum cholesterol level >6.5 mmol/L [251.35 mg/dL] or use of cholesterol-lowering agents). These characteristics were used to predict the presence of renal artery stenosis. A patient was considered to have renal artery stenosis when the angiogram showed at least one stenosis of 50% or more in a renal artery according to the local radiologist.

Model development

Data are presented as a proportion or as the mean ± SD. The univariable association between clinical characteristics and presence of renal artery stenosis was studied by computing the value and 95% confidence interval (CI) of the odds ratio. In a multivariable analysis, clinical characteristics were combined as predictor variables in a logistic regression model predicting the presence of renal artery stenosis (outcome).[27] For each patient in the multivariable analysis, the probability of renal artery stenosis was calculated from the regression model (predicted probability). The reliability, discriminative ability, and validity of the model were assessed. The Appendix gives details on model development and evaluation.

To enable the use of the regression model in clinical practice, a prediction rule was constructed for predicting renal artery stenosis in future patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors. For the presence or level of each clinical characteristic in the regression model, a score was calculated on the basis of the regression coefficients (Appendix). These scores were

added into a sumscore. All possible sum scores and their corresponding predicted probabilities of renal artery stenosis were combined in a graph with 95% CIs of the predicted probabilities.

Role of the funding source

Our funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Statistical Analyses

Angiography was performed in 439 patients with drug-resistant hypertension and 39 patients with an increase in serum creatinine concentration during therapy with ACE inhibitors. The procedure failed in 1 patient. For the remaining 477 patients, angiography showed renal artery stenosis in 107 patients (22%), of whom 90 (84%) had atherosclerotic stenosis and 17 (16%) had fibromuscular dysplasia. Bilateral stenoses were found in 27 of 107 affected patients (25%). Renal scintigraphy was performed in 458 patients; it had a sensitivity of 72% and a specificity of 90% for the diagnosis of renal artery stenosis.

Table 1 shows the univariable distribution of the clinical characteristics for patients with renal artery stenosis and those with essential hypertension. Most clinical characteristics were indicative for renal artery stenosis ($P<0.05$ or borderline significant) except sex, recent onset of hypertension, and presence of advanced hypertensive retinopathy. More young women without signs of atherosclerotic disease were found among patients with fibromuscular dysplasia than among those with atherosclerotic stenosis, but abdominal bruits occurred with the same frequency in both groups (29% and 27%, respectively).

The results of multivariable analysis are also shown in Table 1. Advanced hypertensive retinopathy was not studied any further because this clinical characteristic was missing for 43% of the patients. Data on 11

Table 1. Associations of clinical characteristics with renal artery stenosis.

Clinical characteristic	Patients with renal artery stenosis (n=107)	Patients with essential hypertension (n=370)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (95% CI)†
Mean age±SD, y	57±12	50±12	1.6 (1.3 - 2.0)‡	1.8 (1.3 - 2.6)‡§
Men, %	51	58	0.8 (0.5 - 1.2)	0.4 (0.2 - 0.7)
Black ethnicity, %	1	7	0.1 (0.0 - 0.9)	‖
Atherosclerotic vascular disease,%	63	28	4.5 (2.9 - 7.2)	1.8 (1.0 - 3.3)
Recent onset of hypertension, %	39	34	1.2 (0.8 - 1.9)	1.9 (1.1 - 3.4)
Family history of hypertension, %	57	67	0.7 (0.4 - 1.0)	‖
Ever smoked, %	79	65	2.1 (1.2 - 3.4)	1.6 (1.1 - 2.6)¶
Obesity, %	40	70	0.3 (0.2 - 0.4)	0.4 (0.2 - 0.6)
Abdominal bruit, %	27	4	9.2 (4.6 -18.3)	5.4 (2.4 - 12.2)
Hypertensive retinopathy, %	22	21	1.1 (0.6 - 2.1)	‖
Mean serum creatinine concentration ±SD, µmol/L	112±35	89±22	1.4 (1.2 - 1.5)**	1.4 (1.2 - 1.6)**
Hypercholesterolaemia, %	40	30	1.6 (1.0 - 2.5)	1.7 (0.9 - 3.0)

*Performed in 477 patients.
†Performed in 460 patients.
‡per 10-year increase.
§Value for a patient who never smoked (value depends on smoking history).
‖Not in the multivariable model.
¶Value for a 60-year-old patient (value depends on age).
**Per 10 µmol/L increase.

clinical characteristics of 460 patients were considered predictive of renal artery stenosis. Ethnicity and family history of hypertension were removed from the regression model because their contribution to predicting renal artery stenosis was small. Because renal artery stenosis is believed to be more prevalent in young women and old men, interaction between age and sex was tested; this interaction was not statistically significant (P=0.09). We did include an interaction term between age and smoking because this was the only biologically plausible interaction term that was statistically significant (P = 0.01). This interaction term accounts for the fact that the predictive value of increasing age was stronger for patients who never smoked than for current and former smokers. Finally, the type of standard treatment did not provide additional diagnostic information when it was included in the regression model ($P > 0.2$). The multivariable odds ratios in Table 1 reflect the predictive effect of the individual clinical characteristics while correcting for the other predictors in the multivariable model. For example, the multivariable odds ratio for atherosclerotic vascular disease was lower than the univariable odds ratio because the model also accounted for the effects of age and smoking history.

Model performance

Figure 1 shows the agreement between the predicted and the observed probabilities. For 204 patients (44%), the predicted probability of stenosis was 0% to 10%. The predicted probabilities of stenosis obtained from the model agreed well with the observed frequency of stenosis (goodness-of-fit test, $P > 0.2$). The model discriminated well between patients with renal artery stenosis (predicted probability, 49%±29%) and patients with essential hypertension (predicted probability, 15%±16%): the area under the receiver-operating characteristic (ROC) curve was 0.84 (95% CI, 0.79 to 0.89). Among patients with stenosis, the discriminative ability of the regression model was better for those with atherosclerotic stenosis (predicted probability, 52%±29%) than for those with fibromuscular dysplasia (predicted probability, 34%±26%).

The discriminative ability of the prediction rule differed among the four hospitals that included most of the patients. For these hospitals, the area

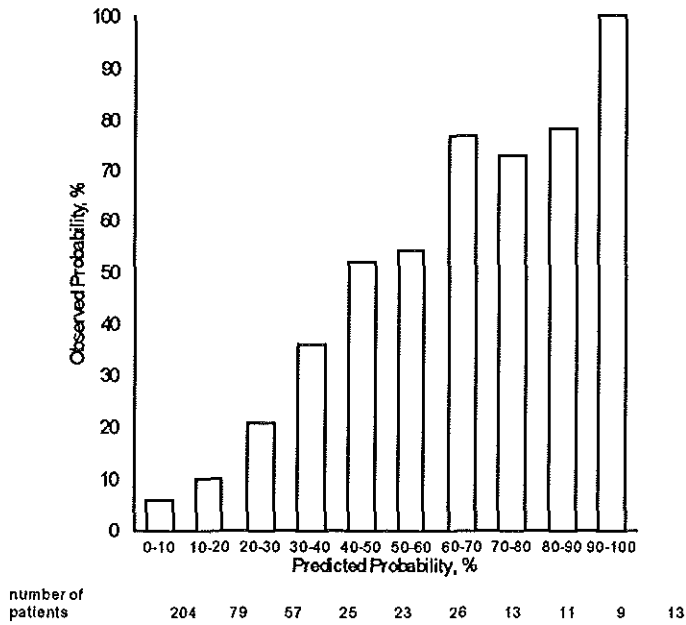

Figure 1. Agreement between the observed probability of stenosis and the probability of stenosis as predicted by the regression model in 460 patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with angiotensin-converting enzyme inhibitors.

under the ROC curve varied from 0.68 to 0.92. This corresponds with the finding that the associations between stenosis and clinical characteristics of patients from these hospitals were not equally strong or were contradictory. For example, atherosclerotic vascular disease was not predictive of stenosis in one hospital and was even more prevalent in patients with essential hypertension in another hospital. This inconsistency may be explained in part by small sample sizes: the number of patients included by these four hospitals were 44, 56, 77 and 151.

Using the model in clinical practice

In the prediction rule for renal artery stenosis, a score was assigned to the level or presence of each clinical characteristic in the regression model (**Table 2**). These scores were added into a sum score that, through the logistic formula, corresponded with a predicted probability of renal artery

Table 2. Prediction rule for quantifying the probability of renal artery stenosis.

Predictor	Score*	
	Persons who never smoked	Former or current smokers
Age†		
20 years	0	3
30 years	1	4
40 years	2	4
50 years	3	5
60 years	4	5
70 years	5	6
Female sex	2	2
Signs and symptoms of atherosclerotic vascular disease‡	1	1
Onset of hypertension within 2 years	1	1
Body mass index <25 kg/m^2	2	2
Presence of abdominal bruit	3	3
Serum creatinine concentration†		
40 µmol/L	0	0
60 µmol/L	1	1
80 µmol/L	2	2
100 µmol/L	3	3
150 µmol/L	6	6
200 µmol/L	9	9
Serum cholesterol level >6.5 mmol/L or cholesterol-lowering therapy	1	1

* The sum score is obtained by adding all relevant scores. The sum score can be used to obtain the predicted probability of renal artery stenosis from Figure 2.

† For intermediate values, the score can be linearly interpolated.

‡ Femoral or carotid bruit, angina pectoris, claudication, myocardial infarction, cerebrovascular accident, or vascular surgery.

stenosis. In **Figure 2**, the predicted probabilities and their 95% CIs can be derived from the sum scores in a graphical manner. For instance, the sum score for a 46-year-old male patient who has smoked in the past; has no

signs or symptoms of atherosclerotic vascular disease; received a diagnosis of hypertension 1 year ago; has a body mass index of 23 kg/m^2, no abdominal bruit, a serum creatinine concentration of 112 µmol/L (91.27 mg/dL) and a serum cholesterol level of 5.4 mmol/L (208.82 mg/dL); and does not take cholesterol-lowering drugs is 11 (4.5+0+0+1+2+0+3.5+0). The scores for age and creatinine concentration were obtained by linear interpolation. **Figure 2** shows that the predicted probability of renal artery stenosis for this patient is 25% (CI, 13 to 43%). The probability can also be calculated by using the formula given in the Appendix.

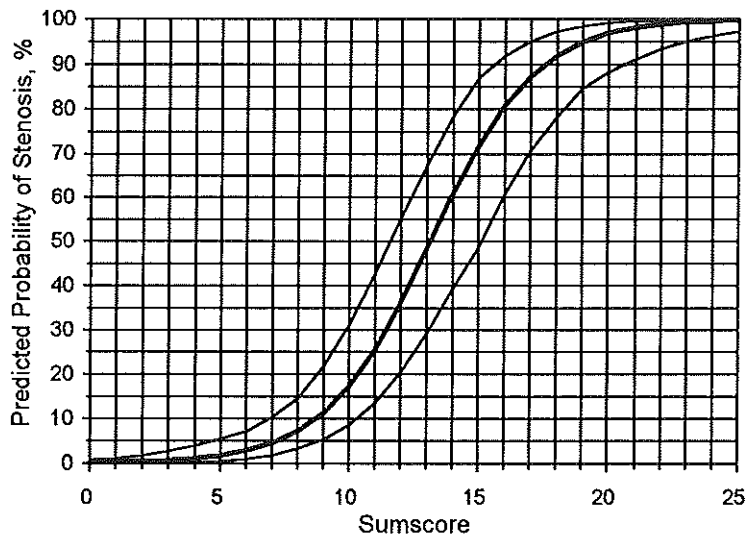

Figure 2. Predicted probability of renal artery stenosis in patients with drug-resistant hypertension as a function of the sum score. The sum score was derived from the prediction rule (Table 2). Thin lines respresent 95% Cis.

The probability of stenosis according to the prediction rule can be used to select patients for renal angiography. If angiography is performed only in patients with a probability of stenosis above a certain cut-off level, the number of angiograms performed in the total group of patients will be reduced. **Table 3** shows the results of using different cut-off levels for the predicted probability of stenosis. The first row in Table 3 gives the scenario

of performing angiography in every patient and therefore identifying all patients with stenosis (sensitivity, 100%). If angiography is performed only in patients whose predicted probability of stenosis is, for example, 10% or more, the number of patients undergoing angiography will be reduced to 61%. However, 1 of every 10 stenoses will be missed (sensitivity, 90%). With increasing cut-off levels, the number of patients undergoing angiography is reduced more and more; as a consequence, however, the number of missed stenoses increases. When a probability of 30% was chosen as the cut-off level, the diagnostic accuracy of the prediction rule (sensitivity, 68%; specificity, 87%) approximated that of renal scintigraphy (sensitivity, 72%; specificity, 90%) in our patient population.

Table 3. Implications of using the prediction rule in clinical practice.

Predicted probability at which angiography is performed	Sensitivity*	Specificity†	Patients undergoing angiography
◄	%		►
≥0	100	0	100
≥10	90	47	61
≥20	81	73	40
≥30	68	87	25
≥40	59	92	20
≥50	44	96	14
≥60	33	98	9
≥70	24	99	6
≥80	17	99	4
≥90	7	100	2

* Patients with stenosis identified by angiography.
† Patients with essential hypertension who did not undergo angiography.

DISCUSSION

We developed a clinical prediction rule to predict the presence of renal artery stenosis from the clinical characteristics of 477 patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors who participated in a prospective study on diagnosis and treatment of renal artery stenosis (the DRASTIC study).[9] By attributing a score to the presence or absence of nine clinical characteristics, a sum score was obtained that corresponded to a probability of renal artery stenosis. The prediction rule proved to be reliable and discriminated well between patients with renal artery stenosis and those with essential hypertension. By applying the prediction rule in clinical practice to select patients for renal angiography, the number of angiograms obtained may have been reduced considerably in a cost-effective manner.

Clinical characteristics have been mentioned before as a means of identifying patients with renal artery stenosis.[16,20-23] Several studies have described the relative frequency of characteristics in patients with renal artery stenosis and those with essential hypertension, such as age, duration of hypertension, atherosclerosis, cigarette smoking, and presence of an abdominal bruit. Some of these clinical characteristics are interrelated, such as those suggestive of atherosclerotic vascular disease. In our multivariable model, we assessed the independent associations between clinical characteristics and the presence of renal artery stenosis. Moreover, our simple prediction rule enables the clinician to quantify the probability of stenosis for any specific patient. Unlike other studies describing schemes for selecting patients suspected of having renal artery stenosis on the basis of their clinical characteristics,[10,11] our study provides quantitative insight in the potential consequences of applying our selection criteria.

The prediction rule predicts the presence of anatomic renal artery stenosis in patients with preserved renal function (serum creatinine concentration ≤200 μmol/L [2.26 mg/dL]), who have drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors. The prediction rule should not be applied if other, secondary causes of hypertension are not adequately ruled out (such as parenchymal renal disease) and should not be applied to patients with

impaired renal function in general. Our study group included some patients who received more medication than the standardized schemes allowed because their blood pressure was very high. Regardless of their blood pressure response to the additional drugs, these patients were considered to be resistant to the standardized regimen and underwent angiography. The prediction rule can therefore be used for patients in whom blood pressure control was achieved with more than two drugs, provided that control could not be achieved on a two-drug regimen. Before introduction on a wide scale, the model must be tested further to establish whether its predictions are valid in other settings.

Although the clinical characteristics of patients with atheroslerotic stenosis and those with fibromuscular dysplasia clearly differ somewhat, the prediction rule can be used to predict the presence of either type of renal artery stenosis. Some clinical characteristics (such as the presence of an abdominal bruit) were found to be relevant for both patients groups, but in other respects (such as signs of atherosclerotic vascular disease), patients with fibromuscular dysplasia resembled those with essential hypertension more closely than they resembled those with atherosclerotic stenosis. Thus, patients with fibromuscular dysplasia are not a distinct group of patients that can be excluded before the prediction rule is applied in clinical practice. For example, only 4 of the 17 patients with fibromuscular dysplasia in our study group were women younger than 40 years of age. We decided not to exclude patients with fibromuscular dysplasia from the analysis because the prediction rule should be applicable to all future patients who present themselves in our clinics. Although the prediction rule performed somewhat better for patients with atherosclerotic stenosis than for patients with fibromuscular dysplasia, the predicted probability in the latter group was significantly higher than that of patients with essential hypertension. Thus, the prediction rule distinguished well between both groups of patients with stenosis and patients with essential hypertension.

In this analysis, anatomical renal artery stenosis was predicted from clinical characteristics. We acknowledge that prediction of functional stenosis (that is, renovascular hypertension) would have been preferable. Unfortunately, no good definition of renovascular hypertension exists. This condition is often defined as being characterized not only by the presence of

renal artery stenosis but also by the cure of the hypertension after repair of the stenosis. However, several factors may explain why relief of renal artery stenosis that has caused hypertension does not always result in cure of hypertension, such as advanced-stage hypertension (third phase of two-kidney one-clip Goldblatt hypertension), technical failure of the intervention, or restenosis. The most important objection to the use of blood pressure response to intervention is that it is a diagnosis made a posteriori. Therefore, the most practical approach is to search for renal artery stenosis instead of renovascular hypertension.

This prediction rule is a practical and simple tool for selecting patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors. To obtain the probability of stenosis for a specific patient, information is needed on nine clinical characteristics; this information is generally readily available in clinical practice. After prespecified scores are added to form a sum score, the corresponding probability of stenosis can be read from a graph. The usefulness of the prediction rule was shown in our data set. The prediction rule was almost as accurate as renal scintigraphy (sensitivity, 72%; specificity, 90%) in predicting renal artery stenosis if angiography was performed in patients for whom the rule predicted a probability stenosis greater than 30%. In contrast to renal scintigraphy, however, the results of the prediction rule are immediately available and free. We therefore conclude that the prediction rule can be used as an alternative for renal scintigraphy in the selection of hypertensive patients for renal angiography, provided that the predictions prove to be valid in other settings. Embedded in the diagnostic work up of hypertensive patients who do not respond well to antihypertensive drugs, the prediction rule can help to reduce the number of negative renal angiograms without missing many patients with renal artery stenosis.

APPENDIX

Model development

Deletion of cases with missing data may cause bias and increases variance.[28] For 40 patients for whom one clinical characteristic was missing, the value was therefore predicted from the other clinical characteristics by multiple regression on values of the other predictors and was subsequently imputed.[28,29] Values for 17 patients for whom more than one value was missing were not imputed because the predicted values for these predictors would have been less reliable. These 17 patients were excluded from the multivariable analysis.

Age and serum creatinine concentration were entered into the logistic regression model as continuous variables. We studied whether transformations of these variables offered a better fit. Smoking was dichotomized as ever or never smoked; the fit of more complex classifications, such as never, past or present smoker or number of pack-years, was also studied. Advanced hypertensive retinopathy was not included in the multivariable analysis because this characteristic was missing in a substantial number of the patients (43%). Nine clinical characteristics were selected for the regression model by backward deletion of the least significant characteristics, done by using the Akaike information criterion:[30] As a result, ethnicity and family history of hypertension were dropped from the model ($P>0.2$). Interaction between clinical characteristics in predicting renal artery stenosis was studied in two ways to control for deviation from the additivity assumption.[28] First, a likelihood ratio test on all first-order interaction terms was performed ($P>0.2$). Second, biologically plausible interaction terms were tested, which led to the inclusion of age x smoking in the model ($P=0.01$).

Model evaluation

The reliability of the regression model was evaluated by the Hosmer-Lemeshow goodness-of-fit test.[27] The discriminative ability of the regression model was evaluated by the area under the ROC curve and its 95% CI.[31,32] The ROC curve is a plot of the false-positive rate (or 1 minus the

specificity) against the true-positive rate (sensitivity), evaluated for consecutive cut-off points of the predicted probability. The area under the ROC curve can be interpreted as the probability that the regression model will assign a higher probability of stenosis to a randomly chosen patient with renal artery stenosis than to a randomly chosen patient with essential hypertension. The area can range from 0.5 to 1 (no to optimal discriminative ability) for sensible models.

The internal validity of the regression model[28,33] was assessed by using bootstrapping techniques, including variable selection.[34] Random bootstrap samples were drawn with replacement from the full sample (200 replications). The discriminative ability of the regression models was determined on the bootstrap samples and on the full sample, in which predictions were based on the regression models fitted on the bootstrap samples. This validation replicates the situation in which the prediction model based on our patients is applied to a group of similar patients. The area under the ROC curve was 0.84 on the full data set and 0.82 after this procedure. Next, four hospitals that included most of the patients were left out of the sample one by one, and regression models were fitted on the remaining data. The discriminative ability of these models was externally assessed on the hospital not included in the fitting procedure. This procedure replicates the situation in which the prediction model is applied in another hospital with a patient population that may be somewhat different.

Derivation of scores in the prediction rule

The multivariable logistic regression model could be written as: predicted probability of stenosis = $1/1+e^{-(LP)}$, where linear predictor LP = -7.859 + 0.059 x age + 0.033 x (75 - age) x ever smoked - 0.996 x sex[female=0, male = 1) + 0.585 x atherosclerotic vascular disease + 0.642 x recent onset - 1.027 x obesity + 1.693 x abdominal bruit + 0.502 x hypercholesterolemia + 0.032 x serum creatinine.

The regression coefficients were multiplied by a shrinkage factor of 0.88, which was derived from bootstrapping procedures. Shrinkage of the regression coefficients aims to improve calibration of predictions in future patients: that is, to prevent low predictions that are too low and high predictions that are too high.[28,35] The intercept was adjusted so that the sum

of predicted probabilities equalled the number of events (106 patients with stenosis in a total of 460 patients). The shrunk formula was:

P(stenosis) = $1/1+e^{-(LP_S)}$, where LP_s = -7.033 + 0.052 x age + 0.029 x (75 - age) x ever smoker - 0.877 x sex(female=0, male=1) + 0.515 x atherosclerotic vascular disease + 0.565 x recent onset - 0.904 x obesity + 1.490 x abdominal bruit + 0.441 x hypercholesterolemia + 0.028 x serum creatinine concentration.

This formula can be used to calculate the exact probability of stenosis. The average SE of the rounded linear predictor was used to calculate the 95% CIs of the predicted probabilities ($1/1+e^{-(LP_S \pm 1.96 \times SE)}$).

For presentation as a prediction rule, the rescaled regression coefficients were multiplied by 2 and were rounded to simplify the computation for clinical practice.

Software

Descriptive analyses were performed with SPSS statistical software (SPSS, Inc., Chicago, Illinois). Imputation of missing values, logistic regression and validation were carried out in the Design Library for S-plus using the transcan, impute, lrm and validate functions.[36]

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CHAPTER 6

INTEROBSERVER VARIABILITY IN THE ANGIOGRAPHIC ASSESSMENT OF RENAL ARTERY STENOSIS

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ABSTRACT

Objective: To assess interobserver agreement in the interpretation of renal angiograms.
Design: Comparison of the assessment of renal angiograms by three experienced radiologists, who evaluated the number of renal arteries and the presence, location, aspect and severity of a renal artery stenosis.
Setting: General hospital and university hospital serving urban and rural populations.
Patients: Patients with difficult-to-treat hypertension referred for diagnostic work-up; 312 angiograms with the intra-arterial digital subtraction technique were obtained from 289 consecutive patients.
Main outcome measures: Interobserver agreement was tested for the following parameters: number of arteries per kidney, presence of stenosis, location of stenosis (truncal, ostial), aspect of stenosis (concentric, eccentric, poststenotic dilatation), severity of stenosis (reduction of lumen diameter in categories of 30%, 40%, etc. to 100%), and overall quality of the angiographic images. Kappa (K) values and weighted K between the three pairs of radiologists were used as estimates of interobserver agreement.
Results: Agreement about the number of renal arteries was reasonable (K=0.50-0.72), as was agreement about the presence of stenosis (K=0.68-0.86). Agreement about stenosis location and aspect was poor (K 0.26-0.47 and K 0.15-0.26, respectively). There was general agreement about the severity of stenosis (weighted K 0.65-0.70), but it was not possible to distinguish between 50% and 60% stenosis or between 60% and 70% stenosis (K<0.40). No correlation was found between agreement on severity of stenosis and the quality of the images.
Conclusions: It is not realistic to make statements about what degree of renal artery stenosis is clinically significant, as long as the intra-arterial angiogram with digital subtraction remains the gold standard. It is likewise risky to rely too strongly on stenosis morphology as visualized by renal angiography, in choosing between balloon angioplasty and stent deployment.

INTRODUCTION

Renal artery stenosis is the most common curable cause of hypertension and may lead to loss of renal function. The decision whether or not to treat renal artery stenosis is influenced by the severity of obstruction. Experimental studies in animals have shown that the cross-sectional area of an artery must be reduced at least 75% before flow is diminished,[1,2] so the degree of stenosis is thought to be of major importance for the functional significance of a stenosis. Furthermore, the risk of total occlusion is greater in arteries with the most severe stenoses.[3-5]

The choice between different treatment modalities, ie, balloon angioplasty, stent insertion or surgery, is sometimes based on the location and type of lesion. Balloon angioplasty is successful in peripheral lesions caused by fibromuscular dysplasia, and in truncal atherosclerotic stenoses. Ostial lesions show a high rate of restenosis after angioplasty,[6,7] probably because the stenosis is part of an atherosclerotic plaque extending from the aorta. Consequently, ostial stenoses are thought to benefit more from arterial stenting or surgical revascularization than from balloon dilatation.

In most clinical centres the final diagnosis of renal artery stenosis is made by intra-arterial angiography in order to assess the degree and location of the stenosis, which is essential for therapeutic policy. Furthermore, renal arteriography is the gold standard for noninvasive techniques such as renal scintigraphy, duplex ultrasonography, magnetic resonance angiography and spiral computed tomographic angiography.

In the present study we determined the interobserver agreement between three experienced radiologists who reviewed 312 renal angiograms obtained in 289 patients with hypertension. About one quarter of these patients had renal artery stenosis.

PATIENTS AND METHODS

Study design

The investigation was part of the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study. The aim of this multicentre study was to optimize the diagnosis and treatment of renovascular hypertension.[8] Patients with hypertension were randomly assigned to one of two standardized antihypertensive drug regimens. Renal angiography was performed in all patients who remained hypertensive (diastolic pressure ≥95 mmHg) after treatment. Patients with atherosclerotic renal artery stenosis with ≥50% reduction of lumen diameter (corresponding to ≥75% reduction of cross-sectional area) and normal renal function were randomly assigned to either balloon angioplasty or medical treatment. A second angiogram was performed after one year. Here we report on the renal angiograms performed between January 1993 and January 1995 in 289 patients (age 52.4±12.2 years, mean±SD; 152 men) at 16 centres. Twenty-three patients underwent angiography twice. Angiograms with intra-arterial contrast injection and digital subtraction were performed via the femoral route by the Seldinger technique with a 5 French catheter. Radiologists from the participating centres were advised to make anteroposterior and antero-oblique images (15-30 degrees) and to use 30-40 ml of non-ionic low-osmolality contrast medium for each series of images (2/sec) with digital subtraction. Selective arteriography was not requested and was performed when the investigator judged it necessary.

Evaluation of renal angiograms

All 312 angiograms were blinded for patient characteristics and hospital source, and were evaluated independently by three experienced vascular radiologists (one working in a large community hospital and two in a university hospital). In order to mimic the usual situation in clinical practice, pre-arrangements regarding diagnostic characteristics and criteria were not made. The radiologists were asked to report on: (1) the number of renal arteries per kidney; (2) the presence of a stenosis of any degree; (3) ostial or truncal location of the stenosis; (4) aspect of the lesion (concentric stenosis,

eccentric stenosis, concentric stenosis with post-stenotic dilatation, eccentric stenosis with post-stenotic dilatation, string-of-beads appearance); and (5) degree of stenosis, subdivided into strata of 10% diameter reduction. Location, aspect and degree were assessed only for stenoses of the main renal artery. The percentage of lumen diameter reduction was estimated without the use of computer-assisted techniques. The radiologists were also asked to judge the technical quality of each study with a score ranging from 1 to 10, 1 indicating completely insufficient quality and 10 perfect quality.

Statistical analysis

Interobserver agreement was expressed using the kappa statistic (K),[9,10] which corrects for the agreement expected by chance alone:

$$Kappa = \frac{proportion\ observed\ agreement - proportion\ expected\ agreement}{1 - proportion\ expected\ agreement}$$

When the agreement between two observers is perfect, the proportion observed agreement is 1 and $K=1$. If the observed agreement is not greater than expected by chance, K will be zero. In general, $K<0.20$ is interpreted as poor agreement, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as good, and >0.80 as very good agreement.[9] To assess interobserver agreement on the degree of stenosis we also calculated weighted K, which takes into account the magnitude of the disagreement between two observers.[10] Because there were three pairs of radiologists, there were three K values for each observation category. All K values are given with their 95% confidence interval (CI).

RESULTS

Technical quality of the angiograms

The angiograms were judged to be of reasonable quality according to the radiologists A, B and C, whose mean judgements amounted to 7.6±1.3, 6.9±1.6 and 7.2±1.7 respectively. There were small differences in quality between the participating hospitals with scores ranging from 6.5±0.9 to 8.0±0.6. Only a small proportion of the angiograms was considered to be of insufficient quality, arbitrarily defined as judgement with a value ≤4. This included 8.2 % of the angiograms according to radiologist A, 8.2 % according to radiologist B and 2.3 % according to radiologist C. These numbers were 6.3%, 6.1% and 0% respectively when only the angiograms with any degree of stenosis were considered.

Number of renal arteries and presence of stenosis

The arteries of 307 right and 312 left kidneys were evaluated. Three patients who had undergone right-sided nephrectomy underwent angiography twice. One renal artery was identified in 86-93% of the kidneys, two renal arteries in 7-13% and three or more in 0-1% of the kidneys (ranges among the three observers; **Table 1**). *K* values for the agreement among the three pairs of observers ranged from 0.50 to 0.72 (**Table 2**). A stenosis in at least one renal artery was observed in 25-38% of the kidneys with *K* values ranging from 0.68 to 0.86.

Location of stenosis

In 113 main arteries all three radiologists were able to diagnose a stenosis and whether it was ostial or truncal. They reported that about one-third of the stenoses were present in the ostium of the renal artery. The remaining two-thirds were located in the truncal part, usually in the proximal segment of the renal artery, and seldom in the mid- or distal segment (data not shown). The scores for location were identical in 71-81% of the arteries (**Figure 1**). The observed agreement was only slightly higher than the expected agreement, indicating that a large proportion of the observed agreement was due to chance. For instance, the observed proportion of

Table 1. Number of renal arteries and presence of renal artery stenosis on 312 angiograms, according to three radiologists.

	Right kidney n=307			Left kidney n=312		
	Radiologist A	Radiologist B	Radiologist C	Radiologist A	Radiologist B	Radiologist C
% of kidneys with 1 artery	87.0	87.3	85.7	92.9	89.4	86.5
% of kidneys with 2 arteries	12.4	12.1	13.4	7.1	10.3	12.8
% of kidneys with ≥3 arteries	0.7	0.7	1.0	0.0	0.3	0.6
% of kidneys with any degree of renal artery stenosis	24.8	28.7	32.9	29.2	31.7	38.1

Table 2. Interobserver agreement between 3 radiologists on the number of renal arteries and on the presence of renal artery stenosis.

	Right kidney n=307		Left kidney n=312	
Radiologist	Number of renal arteries	Presence of any stenosis	Number of renal arteries	Presence of any stenosis
A and B	0.67 (0.61-0.73)	0.82 (0.77-0.86)	0.52 (0.45-0.60)	0.86 (0.82-0.90)
A and C	0.67 (0.61-0.73)	0.68 (0.62-0.74)	0.50 (0.43-0.58)	0.72 (0.66-0.77)
B and C	0.72 (0.67-0.78)	0.69 (0.63-0.75)	0.71 (0.66-0.77)	0.79 (0.74-0.84)

Interobserver agreement was determined with the kappa statistic; numbers in parenthesis are 95 percent confidence intervals.

agreement between radiologists A and C was (8+83)/113=0.805, while the expected proportion of agreement was (24/113)x(14/113) + (89/113)x(99/113)=0.716; *K* was therefore only 0.31 (**Figure 1**). Thus, after correction for chance, interobserver variability about the location of renal artery stenosis was considerable. No relation was found between the technical sufficiency of a certain angiogram and the difference in assessment of location of the stenosis on this angiogram (r = -0.20 or -0.21 for the three pairs).

Aspect of stenosis

There was little agreement on the five categories of aspect of stenosis, with *K* ranging from 0.15 tot 0.26. A string-of-beads was seen in 8-11 of the 113 evaluated arteries (7-10%).

Severity of stenosis

There were 147 main renal arteries in which all three radiologists were able to diagnose a stenosis. Most stenoses were scored as more than 50% reduction of lumen diameter, but there was poor agreement on the exact grading (**Figure 2**). The uncorrected *K* values were 0.35-0.39, and the weighted *K* values were 0.65-0.70 (**Table 3**).

When the stenoses in the major renal artery were divided into only two categories, ie, <50% versus 50-100% stenosis, the number of arteries about which the radiologists had a different opinion ranged from 13 to 21 (mean 17, or 12% of the stenotic arteries). The *K* values for this broad classification were 0.60-0.77 (Table 3). The choice of another cut-off value for stenosis did not influence the interobserver variability. For example, when the categories <70% versus 70-100% were used, *K* ranged from 0.63 to 0.67. Apparently, as the Kappa value is not equal to 1, there are always patients classified by one observer as having a stenosis, and by another as having no stenosis, whichever cut-off value for stenosis is used. Angiogram-quality (mean score of the observer pair) was not correlated to interobserver differences on severity of stenosis for the three pairs of observers, r varied from –0.02 to –0.27.

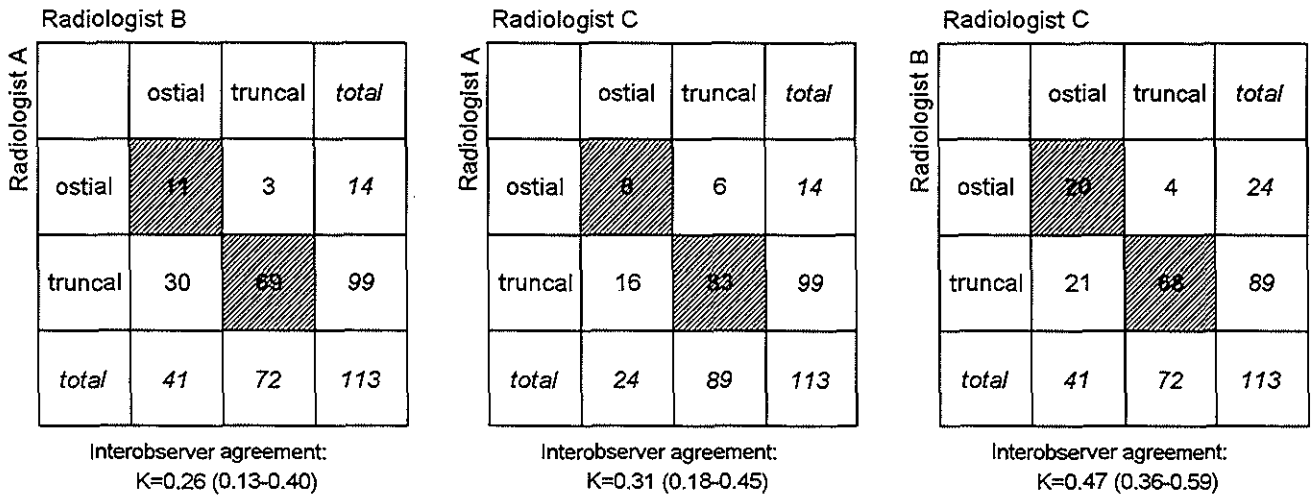

Figure 1. Location of stenosis in 113 main renal arteries, according to three pairs of radiologists. Each number represents the number of main renal arteries with a stenosis.

Radiologist A

Radiologist B	<30	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-99%	100%	total
<30	5	1								6
30-39%	5	2							1	8
40-49%	4	3	2							9
50-59%		7	4	6	2	1		1		21
60-69%			3	3	6	2		1		15
70-79%		2		6	3	4	5	1		21
80-89%	1	1	1	3	2	2	17	4		31
90-99%			1			2	6	5	1	19
100%									17	17
total	15	16	11	18	13	11	28	16	19	147

Radiologist A

Radiologist C	<30	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-99%	100%	total
<30	13	6	2							21
30-39%		2	1							3
40-49%	1	4	3	3						11
50-59%			2	1	2	1	1			7
60-69%				6	7	2				15
70-79%	1	4	2	4	2	3	9			25
80-89%				2	1	3	10	7		23
90-99%				2	1	1	8	5		20
100%			1			1		1	19	22
total	15	16	11	18	13	11	28	16	19	147

Radiologist B

Radiologist C	<30	30-39%	40-49%	50-59%	60-69%	70-79%	80-89%	90-99%	100%	total
<30	5	6	5	4	1					21
30-39%		2		2		1				3
40-49%	1	1	3	5	1					11
50-59%			1	1	1	2	1	1		7
60-69%				4	4	5	2			15
70-79%				3	6	6	5	3		25
80-89%				1		5	15	2		23
90-99%				1	1		8	10		20
100%		1			1			3	17	22
total	6	8	9	21	15	21	31	19	17	147

Figure 2. Degree of stenosis in 147 main renal arteries, according to three pairs of radiologists. Each number represents the number of main renal arteries with a stenosis.

Table 3. Interobserver agreement between 3 radiologists on the severity of renal artery stenosis.

	Main renal arteries with a stenosis n=147	
Radiologist	Grading into 9 categories of diameter reduction: <30%, 30-39%, 40-49%, etc.	Grading into 2 categories of diameter reduction: <50%, 50-100%
A and B	0.39 (0.30-0.47) 0.65 (0.57-0.73)*	0.60 (0.50-0.69)
A and C	0.38 (0.29-0.46) 0.70 (0.62-0.78)*	0.77 (0.70-0.85)
B and C	0.35 (0.26-0.44) 0.66 (0.58-0.74)*	0.66 (0.57-0.75)

* Weighted Kappa
Interobserver agreement was determined with the kappa statistic; numbers in parenthesis are 95 percent confidence intervals.

DISCUSSION

Intra-arterial renal angiography with digital subtraction is widely used for diagnosing renal artery stenosis. In the diagnostic work-up for renovascular hypertension, most clinicians begin with renal scintigraphy or duplex ultrasonography, and, if one of these tests is abnormal, they proceed with angiography. The angiogram is in fact the gold standard against which the diagnostic value of less invasive diagnostic procedures is measured. However, the objectivity of angiography is far from absolute. In our study, even the simple question of whether stenosis is present or absent was not uniformly answered by different radiologists. This is not so much caused by unsatisfactory technical quality of the angiograms, but rather by differences in interpretation.

There are only sporadic reports on renal angiography addressing this issue. One study reported on the agreement with regard to the severity of stenosis among four observers using intravenous digital subtraction

angiography in 134 renal arteries for which the following categories were discerned: 0-49% stenosis, 50-99% stenosis, occlusion, and fibromuscular dysplasia.[11] *K* values ranged from 0.57 to 0.75. A similar result was obtained in a study comparing two observers who assessed 74 renal arteries using the categories of 0-60% stenosis and 61-100% stenosis.[12] In a recent study of balloon angioplasty by Plouin et al,[13] two observers interpreted 178 renal angiograms. They used five categories ranging from no stenosis to total occlusion. *K* values ranged from 0.33 to 0.48 for angiograms performed before and after angioplasty and for follow-up angiograms. Our results are more precise and extend the above observations; when stenoses are classified according to only two categories of severity, interobserver agreement is reasonable, but when more detailed information is required the agreement is poor. It is important to emphasize that, even with the use of broad categories, e.g. stenosis <70% vs stenosis >70%, *K* values were still less than 0.80, which implies that in a substantial percentage of cases radiologists will differ on whether a stenosis is clinically important or not.

As far as we know, no literature data are available on interobserver agreement about the angiographic distinction between ostial and truncal renal artery stenosis. The agreement we found was largely due to chance, with low *K* values. In some centres, the location of the renal artery stenosis determines the type of intervention, in that truncal stenosis is treated by balloon angioplasty, whereas ostial stenosis is treated by stent insertion. The rationale is that, in ostial stenosis, the recurrence rate is high after balloon angioplasty.

Several factors may have influenced the interobserver variability in our study. First, no selection of the angiographic images was made on the basis of the quality of the images; all available images from each session were used for assessment by the three radiologists. This procedure was followed on purpose in order to mimic routine clinical practice. Our finding that interobserver variability was not influenced by the quality of the images implies that our results probably would have been the same had only the good-quality angiograms been analysed.

Second, the examinations were not self-managed by the three evaluating radiologists, whereas in practice the radiologist performing the procedure is also the one making the evaluation. Since the three radiologists shared the

same angiogram, it seems likely that interobserver variation would have been greater if the radiologists themselves had made the angiograms.

Third, there were no pre-arranged criteria on how to measure the degree of stenosis and how to define an ostial lesion exactly, but this again mirrors common practice. It is certainly conceivable that standardized criteria or the use of additional visualization techniques, e.g. CT scanning would improve interobserver agreement. On the other hand, our results may have been flattered by the fact that interobserver agreement on the degree of stenosis and on its location was calculated only for arteries where all three radiologists found a stenosis to be present.

The lack of agreement on the interpretation of angiographic images is well known from other vascular areas, such as the coronary,[14] pulmonary[15] and iliofemoral[16] systems. With respect to coronary and iliofemoral angiography there is extensive experience with quantitative measurements of the minimal lumen diameter and percentage area stenosis by means of computerized edge detection of the stenotic vessel.[17-19] These vessels have the advantage over the renal artery that a proximal reference segment is often available, that post-stenotic dilatation is rare, and that stenotic lesions are often visualized in orthogonal views. Because renal arteries can originate at various angles from the aorta,[20] projection of the origin of the artery is not always sufficient. In spite of these advantages, there is still variability of interpretation due to operator-dependent factors.[18] A recently presented processing technique, specifically developed for renal arteries and using a computerized definition of the reference segment, seems to be a promising refinement.[21]

The most important problems in the diagnostic work-up for renovascular hypertension is the question of how to decide whether or not the stenosis is of clinical significance. Scintigraphic procedures, with or without angiotensin-converting enzyme inhibitor enhancement, are often used to assess the impact of renal artery stenosis on ipsilateral renal function. The diagnostic sensitivity of these procedures is about 70% at a specificity close to 90%.[22,23] It will be difficult to improve on these figures, as long as angiography, as it is now performed in most hospitals, serves as the gold standard. The same can probably be said for techniques that have recently been developed, such as duplex ultrasonography, MR angiography and

spiral CT angiography. The ongoing debate as to what degree of stenosis should be chosen as a cut-off value for significance, e.g. 50%, 60% or 70%, is to our opinion not realistic, because it suggests accuracy where this is an illusion.

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CHAPTER 7

RANDOMIZED CONTROLLED STUDY OF THE EFFECT OF BALLOON ANGIOPLASTY ON HYPERTENSION IN ATHEROSCLEROTIC RENAL ARTERY STENOSIS

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Submitted.

ABSTRACT

Background Percutaneous transluminal balloon angioplasty is widely used for the treatment of renal artery stenosis. However, the long-term impact of this procedure on blood pressure remains to be established in a randomized controlled setting. The Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study sought to determine whether balloon angioplasty affords any advantage over antihypertensive drug therapy for control of blood pressure.

Methods The DRASTIC study is a prospective randomized multicenter study of 1205 patients with hypertension, with the aim to develop a strategy for optimizing diagnosis and treatment of renovascular hypertension. In this report, balloon angioplasty was compared with antihypertensive medication in 106 patients with atherosclerotic renal artery stenosis and a serum creatinine level ≤2.26 mg/dL (200 μmol/L). These subjects had been referred for renal angiography because they had a diastolic blood pressure ≥95 mmHg despite treatment with a standardized two-drug regimen, or exhibited a rise in serum creatinine ≥0.23 mg/dL (20 μmol/L) during angiotensin converting enzyme inhibitor treatment. In the patients randomized to medication (n=50), the treatment regimen was expanded according to a stepwise protocol to include three or more drugs; patients who remained hypertensive at 3 months underwent balloon angioplasty. In the group randomized to balloon angioplasty (n=56), medication was administered, if necessary, according to the same stepwise protocol. Outcome measures were blood pressure and number and doses of antihypertensive drugs (defined daily doses, DDDs) at 3 and 12 months. Changes in renal function were also investigated. Patients who completed the study underwent repeat angiography at 12 months.

Results At 3 months blood pressure was comparable in the two treatment arms (169±28/99±12 mmHg with balloon angioplasty vs 176±31/101±14 mmHg with medication, NS). The number of DDDs was 2.1±1.3 in the balloon angioplasty group and 3.2±1.5 in the medication patients (P<0.001). At 12 months, no significant differences between the angioplasty group and the medication group were seen in either blood pressure (160±26/93±13 vs 163±25/96±10 mmHg, respectively) or DDDs (2.5±1.7 vs 3.1±2.3, respectively). In the angioplasty group, restenosis was found in 48% of repeat angiograms but the blood pressure response did not differ between patients with and without restenosis. In the medication group, 22 patients underwent balloon angioplasty because of persistent

hypertension. Blood pressure fell after balloon angioplasty but remained higher than in patients who did not undergo balloon angioplasty. A beneficial effect of balloon angioplasty could only be identified when a combination of blood pressure and drug use was considered, and not on the basis of the absolute blood pressure levels. At 3 months, creatinine clearance was 70±25 mL/min in the angioplasty group vs 59±23 mL/min in the medication group (P=0.03), and at 12 months it was 70±24 vs 62±27 mL/min (P=0.11). At 3 months, the prevalence of an abnormal scintigram was 36% vs 70% (P=0.002), and at 12 months it was 36% vs 57% (P=0.04).

Conclusions In terms of blood pressure control, balloon angioplasty offers little advantage over medication in patients with atherosclerotic renal artery stenosis. Balloon angioplasty had a favorable effect on renal function tests as compared with medication alone, but the clinical importance of this difference is uncertain. At present, balloon angioplasty should be restricted to patients who remain hypertensive despite treatment with three or more drugs.

INTRODUCTION

The animal experiments of Goldblatt and colleagues[1] on the effects of renal artery constriction led to the recognition of renal artery stenosis as a cause of hypertension. Initially, surgical revascularization was the only treatment for stenosis.[2,3] Since the advent of percutaneous transluminal renal angioplasty or balloon angioplasty,[4] with or without stent placement, this procedure has supplanted surgery as the preferred treatment.[5] Because balloon angioplasty is relatively non-invasive and conceptually attractive, it is widely used. Uncontrolled retrospective studies show a partial response in 36 to 100% of cases, with the highest response rates seen in fibromuscular dysplasia.[6] Complete cure of the hypertension is seen in only a few patients.

Two randomized small-scale studies suggest that the uncontrolled reports have overestimated the effect of balloon angioplasty on blood pressure and that the general enthusiasm for this procedure may not be justified.[7,8] Studies performed thus far can be criticized for various shortcomings; most importantly, there is no uniform definition of a partial blood pressure response and re-angiography to assess recurrence of stenosis is not systematically performed.[6]

Here we report on a multicenter randomized controlled study of balloon angioplasty vs medical treatment in patients with atherosclerotic renal artery stenosis associated with hypertension and normal or mildly impaired renal function.

METHODS

The Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study is a prospective randomized trial conducted at 26 centers in the Netherlands between January 1993 and November 1998. The design of the study has been described elsewhere.[9] The present report addresses the therapeutic phase of the trial, in which patients with atherosclerotic renal artery stenosis were randomized to balloon angioplasty or conservative antihypertensive treatment. The study was approved by the institutional review board at each participating center. All patients provided written

informed consent.

Patient population and randomization

In total, 1205 patients, 51.2±12.4 yr (mean±SD), serum creatinine 0.97 (0.45-2.25) mg/dL (median, range), were included in the DRASTIC study. These patients were assigned to a standardized drug regimen, ie, in patients ≤40 yr either amlodipine 10 mg or enalapril 20 mg, and in patients >40 yr either amlodipine 10 mg plus atenolol 50 mg or enalapril 20 mg plus hydrochlorothiazide 25 mg. Expressed as defined daily doses (DDDs, one DDD being the assumed average maintenance dose per day for a drug used on its main indication in adults),[10] these regimens correspond with 2.0-3.0 DDDs. Eight percent of the patients were treated with other drug regimens, because of contra-indications or adverse effects of the above medications, but these patients followed the same treatment principle of one drug if they were ≤40 yr and two drugs if they were >40 yr with equally effective agents.

Renal arteriography was performed in 543 patients because diastolic blood pressure, measured at 3 consecutive visits, remained ≥95 mmHg despite treatment with the standardized regimens, or because serum creatinine at the second or third visit had risen by ≥0.23 mg/dL (20 µmol/L) during angiotensin converting enzyme (ACE) inhibitor therapy. In this way 169 patients with renal artery stenosis (≥50% reduction of lumen diameter) were identified, 25 of them with ACE inhibition-related renal function impairment. Patients were excluded from the treatment phase of the study if they had any of the following: a single functioning kidney with serum creatinine >1.70 mg/dL (150 µmol/L), length of affected kidney <8.0 cm on ultrasound, total occlusion of the renal artery, aortic aneurysm necessitating surgery, or renal artery stenosis due to fibromuscular dysplasia.

Eligible patients were allocated to balloon angioplasty or medical treatment by block randomization, balancing over strata and over institutions.[11] Stratification variables were serum creatinine (<1.36 vs ≥1.36 mg/dL [120 µmol/L]), type of antihypertensive medication taken during the diagnostic phase of the study (amlodipine/atenolol vs enalapril/hydrochlorothiazide), and unilateral vs bilateral renal artery stenosis. Allocation concealment was ensured by computer-mediated

randomization at the coordinating center (University Hospital Rotterdam).

Treatment and follow-up

Patients assigned to the medication group and, if necessary, those assigned to the angioplasty group, received antihypertensive drug therapy according to a stepwise protocol aiming at a target diastolic blood pressure <95 mmHg. The treatment regimen consisted of whichever drugs the patient had been receiving at the time of randomization. If blood pressure was not controlled with a two-drug regimen, the recommended next step was to add hydrochlorothiazide as a third drug for patients receiving amlodipine plus atenolol and to add amlodipine for patients treated with enalapril plus hydrochlorothiazide. In some patients, doxazosin 4 mg was added as a third or fourth drug. Blood pressure was measured according to the recommendations of the American Society of Hypertension, every 1 to 3 months.[12] Three and 12 months after randomization blood pressure was also measured with an automatic device (Datascope, Datascope Corporation, Montvale, NJ), at 5-min intervals over a 60-min period. Also at 3 and 12 months, serum creatinine was determined and renal scintigraphy after captopril challenge[13] was performed. In both the angioplasty and medical treatment groups, a repeat renal angiogram was made at 12 months.

Patients assigned to balloon angioplasty were given aspirin, 300 mg daily, starting 1 day prior to balloon angioplasty and continuing for 6 months after balloon angioplasty. Antihypertensive drug treatment was discontinued on the day of the procedure to prevent the occurrence of hypotension after the procedure, and was re-instituted if necessary. If, after 3 months, diastolic pressure was ≥95 mmHg or serum creatinine had risen by ≥0.23 mg/dL (20 μmol/L), the treating physician was permitted to decide whether or not to proceed to a second balloon angioplasty, stent deployment, or bypass surgery.

In the group allocated to medical treatment, balloon angioplasty was performed if, after 3 months, diastolic pressure was ≥95 mmHg despite treatment with ≥3 drugs. Balloon angioplasty was also performed if there was clear biochemical or scintigraphic evidence of progressive renovascular occlusive disease as indicated by a marked rise of serum creatinine (≥0.23 mg/dL [20 μmol/L]) or a virtually flat renogram.

Renal arteriography and renal scintigraphy

Arteriography was performed via the femoral approach using the digital subtraction technique. Images were assessed in each participating center by the radiologist who had obtained the arteriogram. Reduction of lumen diameter of the renal artery by ≥50% was diagnosed as renal artery stenosis. All arteriograms were subjected to additional evaluations by three independent radiologists, who scored all images for grade of stenosis (categories of 10% lumen reduction). The median value of these three scores is referred to as 'panel judgement'.

Renal scintigrams were obtained with the use of ^{99m}Tc-labeled mertiatide (mercaptoacetyltriglycine [^{99m}Tc-MAG$_3$]). The nuclear medicine physicians who assessed the renal scintigrams were asked to report the results as high probability, low probability, or indeterminate, as indicated in the consensus report on renal scintigraphy.[14] High probability and indeterminate outcomes were considered to be 'abnormal scintigrams'.

Outcome measures

Primary outcome measures were systolic and diastolic blood pressure and number and doses of antihypertensive drugs at 3 and 12 months after randomization. Secondary outcome measures were: serum creatinine, creatinine clearance (according to the Cockroft-Gault formula) at 3 and 12 months, the presence of an abnormal renal scintigram at 3 and 12 months, the arteriographic patency of the renal artery (<50% lumen diameter reduction) at 12 months, and the incidence of complications.

Statistical analysis

The study was designed to have 48 patients per group, in order to have a power of 80% to detect a blood pressure response difference of 30 percentage points (improvement in 70% of patients in the angioplasty group and in 40% in the medication group), at a 5% level of significance with one-sided tests. Results are given as mean±SD or median and range. Comparisons between groups were made with Student's *t* test or the Mann-Whitney test. Chi-square test was used for categorical data. A paired *t* test

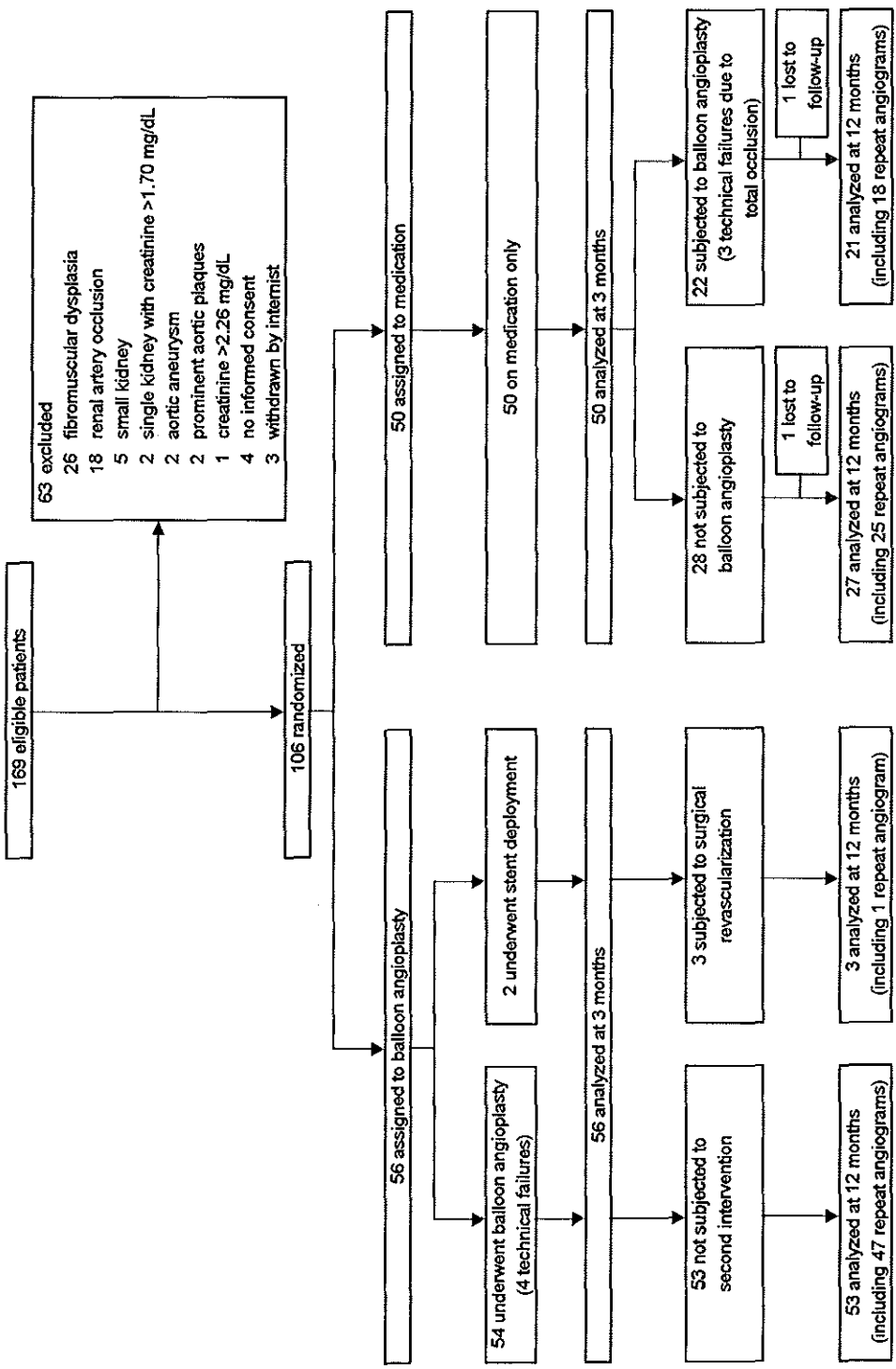

Figure 1. Study profile.

was used to compare the follow-up blood pressure levels with the levels at entry.

RESULTS

Of the 169 eligible patients, 53 were excluded for pre-specified reasons (**Figure 1**). Ten patients could not be randomized for other reasons, ie, high risk of angioplasty-related complications due to extensive aortic plaque formations (n=2), rise of serum creatinine to 2.51 mg/dL (222 μmol/L) during drug treatment (n=1), absence of informed consent (n=4), and balloon angioplasty before referral to the coordinating center (n=3). Thus, 106 patients were randomized, 56 for balloon angioplasty and 50 for medication (Figure 1). During follow-up, 42 patients were using the same type of drugs as before randomization, and 41 patients were using at least one drug that they also had been using before randomization. The remainder were on other drug combinations, except for 4 patients of the angioplasty group, to whom no antihypertensive drugs were prescribed after the intervention. Blood pressure levels and doses of antihypertensive drug treatment (means of the three pre-randomization visits) were comparable in the angioplasty and medication groups, as were other baseline characteristics (**Table 1**). Likewise, in the subgroup with ACE inhibition-related impairment of renal function, the patients allocated to balloon angioplasty had blood pressure levels and drug doses that were similar to those in the patients allocated to medication.

Renal arteriography

According to the panel judgement, ≥50% lumen diameter reduction of the renal artery was present on the right side in 27 patients, on the left side in 46 patients (2 of whom had a single functioning kidney), and bilaterally in 23 patients (5 of whom had unilateral total occlusion). A lumen diameter reduction <50% was found in 10 patients (5 of whom were randomized to the angioplasty group and 5 to the medication group).

Of the 56 patients in the angioplasty group, 2 underwent additional stent placement, one because of a small aneurysm distally in the renal artery, and

Table 1. Baseline characteristics and risk factors in the patients randomized for balloon angioplasty vs medication.*

	Balloon angioplasty (n=56)	Medication (n=50)
Clinical data		
Male sex — no. (%)	37 (66%)	28 (56%)
Age — yr	59.4±10.2	61.4±9.8
Body mass index — kg/m^2	25.4±3.5	25.2±3.1
Cigarette smoking ever — no. (%)	46 (82%)	35 (70%)
Cigarette smoking — median packyears (range)	18.7 (0-48)	13.4 (0-66)
Abdominal bruit — no. (%)	12 (21%)	12 (25%)
Diabetes mellitus — no. (%)	3 (5%)	3 (6%)
Onset of hypertension <2 yr — no. (%)	19 (34%)	17 (34%)
Systolic blood pressure — mmHg	179±25	180±23
Diastolic blood pressure — mmHg	104±10	103±8
Quantity of antihypertensive drugs		
DDDs	3.3±1.1	3.2±1.5
number of drugs	2.0±0.8	2.0±0.9
Amlodipine/atenolol vs enalapril/HCl-thiazide regimen — no. vs no.	18 vs 22	13 vs 23
Laboratory data		
Serum creatinine —mg/dL		
mean±SD	1.27±0.38	1.33±0.36
Creatinine clearance — mL/min	60±24	67±23
Cholesterol — mmol/L	6.3±0.8	6.4±1.2
Cholesterol >6.5 mmol/L — no. (%)	22 (39%)	18 (40%)
Prevalence of abnormal renal scintigrams — no./no. (%)	35/54 (65%)	32/49 (65%)
Inclusion data		
Hypertension resistant to standardized medication — no. (%)	49 (87%)	38 (76%)
ACE inhibitor-related renal function impairment — no.(%) †	7 (13%)	12 (24%)

*Plus-minus values are means±SD.

†In the subgroup with ACE inhibitor-related renal function impairment, blood pressure was 164±25/98±10 mmHg in the angioplasty group and 160±20/98±5 mmHg in the medication group, on 2.9±0.4 and 2.9±1.1 DDDs respectively.

the other because the radiologist did not adhere to the protocol. Balloon angioplasty failed for technical reasons in 3 patients with unilateral stenosis, and on one side in a patient with bilateral stenosis. After 3 months, surgical revascularization was performed in 2 of these patients as well as in a third patient with persistent hypertension (diastolic pressure ≥95 mmHg).

A repeat angiogram as obtained 12 months after balloon angioplasty in 48 of 56 patients. Four patients refused re-angiography, and repeat angiograms were not requested for 3 patients with technical failure of balloon angioplasty and one patient who underwent surgical revascularization. Of the 48 repeat angiograms, 23 showed ≥50% lumen diameter reduction of the treated artery but none demonstrated progression to total occlusion.

Of the patients in the medication group, 28 were treated exclusively with antihypertensive medication during the 12-month follow-up period. In the remaining 22 patients, balloon angioplasty was performed after 3 months because of persistent hypertension despite treatment with three or more drugs (n=14), or because of evidence of progressive renovascular occlusive disease. It was necessary to abort this procedure in three patients (one of whom had been treated with enalapril) when the arteriogram revealed progression to total occlusion. One of these three patients subsequently underwent surgical revascularization, which failed to improve blood pressure or renal function.

A repeat angiogram was obtained 12 months after randomization in 43 of the 50 patients initially randomized to the medication group. One patient died of a cerebral infarction before the end of the study, one patient withdrew from follow-up, and 5 patients refused re-angiography. Progression of the stenosis to total occlusion was observed in a total of 4 of the 43 patients (9%), including the 3 patients mentioned above.

Blood pressure

Blood pressure levels are presented in **Table 2**. On average, blood pressure at 3 months did not differ between the angioplasty and medication groups. Intention-to-treat analysis at 12 months revealed no significant differences in blood pressure between the medication group, 44% of whom underwent balloon angioplasty after 3 months, and the angioplasty group

Table 2. Results of treatment in patients randomized for balloon angioplasty vs medication.*

	Balloon angioplasty (n=56)	Medication (n=50)	*P*
3 Months			
Systolic blood pressure — mmHg	169±28†	176±31†	0.25
Diastolic blood pressure — mmHg	99±12†	101±14†	0.36
Systolic blood pressure by automatic device — mmHg	160±26	163±27	0.61
Diastolic blood pressure by automatic device — mmHg	89±14	88±13	0.73
Quantity of antihypertensive drugs			
DDDs	2.1±1.3	3.2±1.5	<0.001
number of drugs	1.9±0.9	2.5±1.0	0.002
Serum creatinine —mg/dL			
mean±SD	1.19±0.29	1.33±0.43	0.05
Creatinine clearance — mL/min	70±25	59±23	0.03
Prevalence of abnormal renal scintigrams — no./no. (%)	17/47 (36%)	28/40 (70%)	0.002
12 Months			
Systolic blood pressure — mmHg	160±26‡	163±25‡	0.51
Diastolic blood pressure — mmHg	93±13‡	96±10‡	0.25
Systolic blood pressure by automatic device — mmHg	152±20	162±27	0.07
Diastolic blood pressure by automatic device — mmHg	84±10	88±13	0.13
Quantity of antihypertensive drugs			
DDDs	2.5±1.7	3.1±2.3	0.10
number of drugs	1.9±0.9	2.4±0.9	0.002
Serum creatinine —mg/dL			
median (range)	1.18 (0.59-1.91)	1.24 (0.57-8.21)§	0.11
Creatinine clearance — mL/min	70±24	62±27	0.11
Prevalence of abnormal renal scintigrams — no./no. (%)	19/53 (36%)	25/44 (57%)	0.04
Complications			
Occlusion of the affected artery	--	8%	
Rupture of the affected artery	--	--	
Rise in serum creatinine ≥50%	2%	6%	
Cholesterol cristal-embolisation	--	2%	
Groin hematoma necessitating transfusion or surgery	2%	4%	
Other	2%	4%	

*Plus-minus values are means±SD.
†*P* <0.05 for comparison with blood pressure at entry for angioplasty group, *P* >0.10 for medication group.
‡*P* <0.005 for comparison with blood pressure at 3 months for both groups
§Serum creatinine had a nonparametric distribution in this group.
¶Symptomatic hypotension at the time of angioplasty in the angioplasty group (1 case), angio pectoris and myocardial infarction in the medication group (2 cases).

(Figure 1). Antihypertensive drug doses were lower in the angioplasty group than in the medication group at 3 months (2 vs 3 DDDs, respectively) but this difference was not sustained at 12 months. Similarly, in the subgroup with ACE inhibitor-related renal function impairment, blood pressure levels at 3 and 12 months were comparable in the medication and angioplasty arms.

In **Table 3**, the results in patients randomized to medication are analyzed according to whether they underwent balloon angioplasty after 3 months or continued conservative therapy for the duration of the study. Blood pressure was higher in patients who underwent balloon angioplasty after 3 months than in those who remained on medication alone. Blood pressure improved after balloon angioplasty but was still higher at 12 months than in patients who were treated with medication alone. DDDs did not change after balloon angioplasty and at 12 months were no different from those in the group on medication alone.

Improvement (defined as either a ≥10 mmHg decrease in diastolic pressure with an unchanged or reduced number of drugs, or a reduction in the number of drugs accompanied by no change or a ≥10 mmHg decrease in diastolic pressure) was observed at 12 months in 38 of the 56 patients in the angioplasty group and in 18 of the 48 patients in the medication group. Worsening (defined as either a ≥10 mmHg increase in diastolic pressure with an unchanged or increased number of drugs, or an increase in the number of drugs associated with no change or a ≥10 mmHg increase in diastolic pressure) was noted at 12 months in 5 patients in the angioplasty group and in 16 in the medication group. The difference in favor of balloon angioplasty was statistically significant (P=0.002). If the number of drugs is replaced by the number of DDDs in these definitions, then improvement at 12 months could be documented in 40 of the 56 patients in the angioplasty group and in 16 of the 48 patients in the medication group, while worsening occurred in 4 members of the angioplasty group and 11 of the medication group (P<0.001). Thus, the trend in favor of balloon angioplasty remained significant with these alternative definitions. Cure of hypertension, defined as diastolic blood pressure <95 mmHg without antihypertensive drug treatment, was observed in 4/56 (7%) of the patients of the angioplasty group and in none of the patients in the medication group.

Table 3. Results of treatment in patients randomized to medication. results in patients subjected to balloon angioplasty after 3 months vs patients remaining on medication only.*

	Balloon angioplasty after 3 Months (n=22)	Medication Only (n=28)	*P*
At entry			
Systolic blood pressure — mmHg	185±22	176±24	0.21
Diastolic blood pressure — mmHg	107±7	101±9	0.02
Quantity of antihypertensive drugs			
DDDs	3.6±1.8	2.8±0.9	0.05
number of drugs	2.3±1.0	1.8±0.8	0.08
Serum creatinine —mg/dL			
mean±SD	1.37±0.36	1.30±0.37	0.56
Creatinine clearance — mL/min	55±21	63±26	0.22
Prevalence of abnormal renal scintigrams — no./no. (%)	14/21 (67%)	18/28 (64%)	0.86
3 Months			
Systolic blood pressure — mmHg	190±33	164±24	0.004
Diastolic blood pressure — mmHg	111±13	94±9	<0.001
Quantity of antihypertensive drugs			
DDDs	3.7±1.6	2.8±1.2	0.03
number of drugs	2.8±1.1	2.2±0.8	0.02
Serum creatinine —mg/dL			
mean±SD	1.30±0.38	1.36±0.45	0.65
Creatinine clearance — mL/min	58±21	60±24	0.75
Prevalence of abnormal renal scintigrams — no./no. (%)	10/16 (63%)	18/24 (75%)	0.49
12 Months			
Systolic blood pressure — mmHg	169±25†	159±24‡	0.16
Diastolic blood pressure — mmHg	102±9†	91±9‡	<0.001
Quantity of antihypertensive drugs			
DDDs	3.3±2.8	3.0±1.8	0.74
number of drugs	2.5±1.1	2.4±0.8	0.81
Serum creatinine —mg/dL			
median (range)	1.28 (0.60-8.21)§	1.22 (0.57-1.99)	0.33
Creatinine clearance — mL/min	58±26	65±27	0.42
Prevalence of abnormal renal scintigrams — no./no. (%)	10/19 (53%)	15/25 (60%)	0.63

*Plus-minus values are means±SD.
†*P* <0.001 for comparison with blood pressure at 3 months.
‡*P* >0.20 for comparison with blood pressure at 3 months.
§Serum creatinine had a nonparametric distribution in this subgroup.

In the 52 patients of the angioplasty group in whom balloon angioplasty was technically successful, including the 2 patients who underwent additional stent deployment, neither the blood pressure response nor the antihypertensive drug doses were related to the severity of renal artery stenosis at randomization (**Figure 2**). There were also no correlations between blood pressure response or drug doses and the presence or absence of residual stenosis (≥50% lumen diameter reduction) after 12 months. Blood pressure was 161±20/90±8 mmHg on 2.2±1.2 DDDs in the 23 patients with residual stenosis, as compared with 159±32/96±16 mmHg on 2.9±2.0 DDDs in the 25 patients without stenosis (P>0.10 for systolic pressure and diastolic pressure as well as for medication). In the angioplasty group, the presence of an abnormal scintigram at entry did not predict the blood pressure response; there were no differences in blood pressure or in DDDs between patients with a normal scintigram at entry and patients with an abnormal scintigram (**Figure 3**).

Renal function and scintigram

At 3 months, creatinine clearance was higher in the angioplasty group than in the medication group (Table 2). The prevalence of abnormal scintigrams at 3 months was lower in the angioplasty group than in the medication group. At 12 months, creatinine clearance remained higher and the prevalence of abnormal scintigrams remained lower in the angioplasty group than in the medication group, despite the fact that approximately 40% of patients in the medication group had undergone balloon angioplasty after 3 months.

DISCUSSION

The aim of this randomized controlled study was to determine whether balloon angioplasty affords any advantage over medication in the treatment of hypertension associated with atherosclerotic renal artery stenosis. Our results show that, in terms of blood pressure control, balloon angioplasty may eliminate the need for one antihypertensive drug given in its usual daily dose. Similar blood pressure levels were reached in the angioplasty and

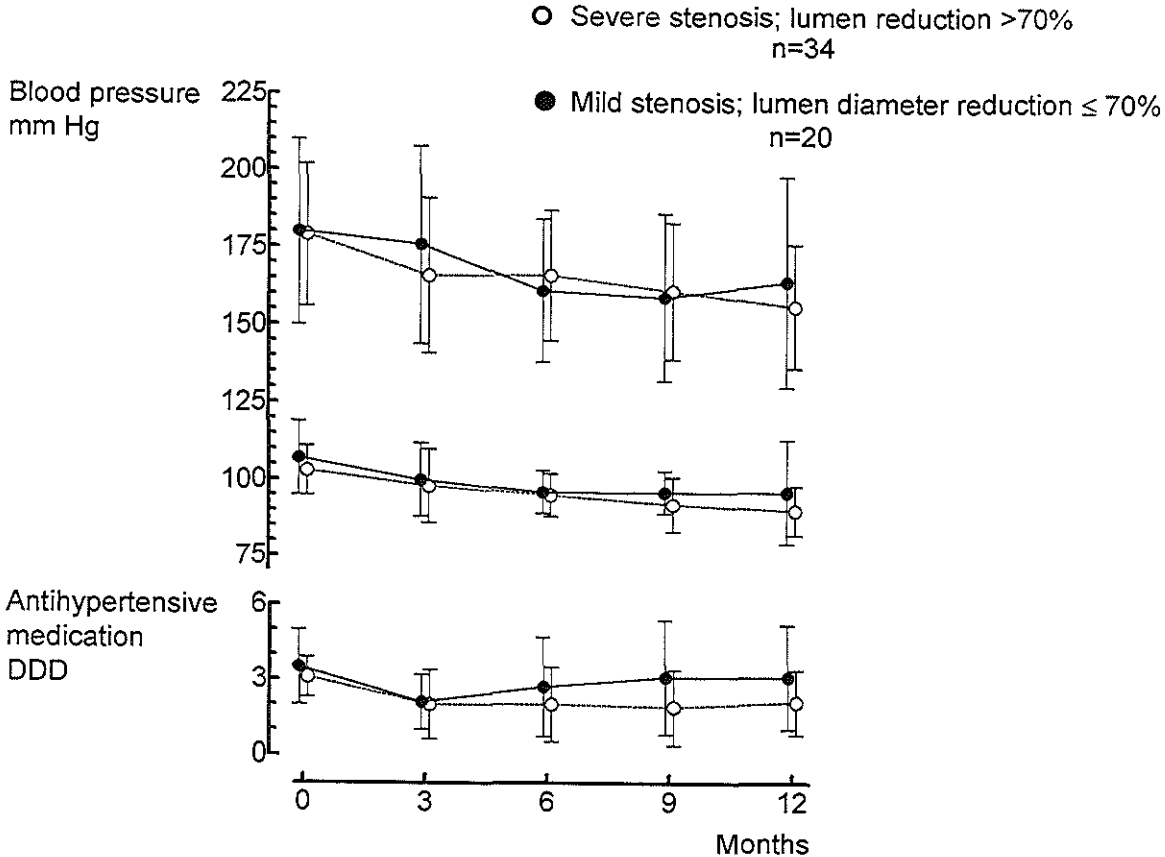

Figure 2. Blood pressure (mean and SD) in the balloon angioplasty group after technically successful balloon angioplasty. Results in patients with severe stenosis vs patients with mild stenosis.

Included are 2 patients with technically failed angioplasty who later underwent surgical revascularization.

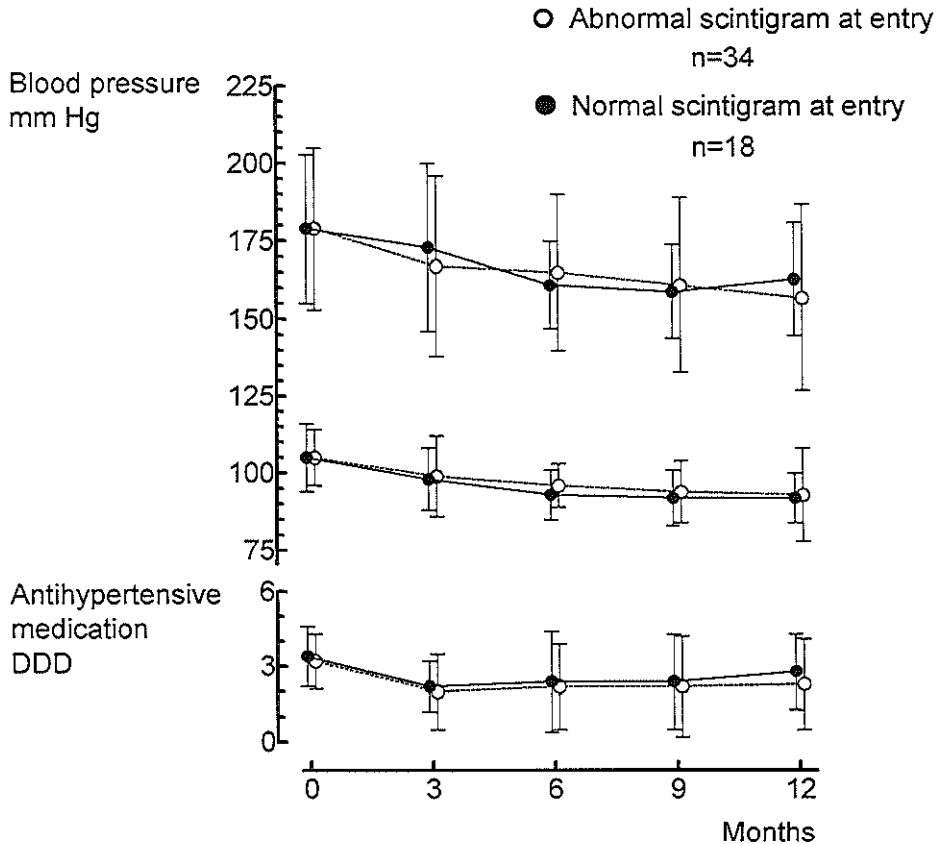

Figure 3. Blood pressure (mean and SD) in the angioplasty group after technically successful balloon angioplasty. Results in patients with an abnormal renal scintigram at entry vs patients with a normal scintigram.
Included are 2 patients with technically failed angioplasty who later underwent surgical revascularization. In 2 patients the scintigram was missing.

medication groups. In our study, very few patients were completely cured by balloon angioplasty. Balloon angioplasty had a favorable effect on renal function, as indicated by a fall in serum creatinine and improvement of creatinine clearance and the renal scintigram.

A number of reasons may account for the rather limited antihypertensive efficacy of balloon angioplasty. Balloon angioplasty is known for its high incidence of restenosis,[15-17] and this may adversely affect the blood pressure response. Our study, however, showed no difference in blood pressure response between patients with and without restenosis. Stent placement has been shown to reduce the incidence of restenosis[18,19] but, in light of our results, it is doubtful whether this will improve the blood pressure response.

Another explanation for the disappointingly small effect of balloon angioplasty on blood pressure in our study may be related to the fact that approximately 40% of patients in the medication group underwent balloon angioplasty after 3 months. Complete follow-up data on medication without balloon angioplasty were therefore only available at 3 months. When the patients who had been initially assigned to the medication group but later underwent balloon angioplasty were evaluated as a separate subgroup, it appeared that balloon angioplasty indeed had a favorable effect on blood pressure. However, blood pressure at 12 months in the medication group as a whole was not higer than in the angioplasty group. The number of drugs and doses of drugs at 12 months also did not differ significantly between the medication and angioplasty groups. Our results, therefore, do not argue against the more conservative management strategy as followed in the patients randomized for medication, ie, extension of drug treatment and proceeding to balloon angioplasty only if after 3 months the patient is still hypertensive on ≥3 drugs or a rise of serum creatinine and worsening of the renal scintigram are providing evidence of progressive renovascular disease.

Our method of patient selection may also have contributed to the results. In 10 of the 106 patients, 5 in the angioplasty group and 5 in the medication group, the lumen diameter reduction of the renal artery on the arteriogram was judged to be <50% by an independent panel of three experienced radiologists. Some investigators consider a stenosis to be hemodynamically significant only if the diameter reduction is >60%[20,21] or >70%.[22,23] However, we did not observe a difference in blood pressure response

between patients with ≤70% lumen diameter reduction and patients with >70% reduction.

Our study was aimed primarily at assessing the influence of balloon angioplasty on blood pressure control but it also provides some information about the effect of this intervention on the kidney. Balloon angioplasty increased creatinine clearance and improved the renal scintigram. The long-term benefits from these actions, in terms of mortality and morbidity, remain to be established.

We conclude that the effect of balloon angioplasty on blood pressure is too small to justify the commonly held opinion that balloon angioplasty is preferable to medication alone in most patients with hypertension associated with atherosclerotic renal artery stenosis. It is still prudent policy to restrict balloon angioplasty (with or without stent deployment) to patients who remain hypertensive despite treatment with ≥3 drugs and to patients with progressive renovascular disease as evidenced by parameters of renal function. Renal function tests are improved after balloon angioplasty, as compared with medication alone. The clinical significance of this favorable effect of balloon angioplasty on the kidney is unclear but it may well prove to be more important than the effect of the procedure on blood pressure.

APPENDIX

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CHAPTER 8

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

The study described in this thesis was performed (1) to define the optimal strategy to diagnose renal artery stenosis, and (2) to evaluate the effect of balloon angioplasty on blood pressure in patients with atherosclerotic renal artery stenosis. In this chapter the merits and shortcomings of the different parts of the study are discussed and the major conclusions are summarized. Some practical recommendations will also be given.

As described in **Chapter 2**, the diagnostic accuracy of renal scintigraphy was disappointing. When the specificity was set at 0.90, which in our opinion is a minimum requirement, the sensitivity was only 0.65 for DTPA scintigraphy without captopril challenge and 0.68 for DTPA scintigraphy after captopril challenge. Receiver operating characteristic (ROC) curves were constructed for the single-kidney fractional uptake (left-to-right contribution) as diagnostic parameter. The ROC curves were similar for DTPA with and without captopril challenge, indicating that the use of captopril did not offer any advantage. MAG_3 scintigraphy was not better than DTPA scintigraphy in terms of accuracy, whereas the interpretation of MAG_3 scintigraphy was more complicated than that of DTPA scintigraphy.

When renal scintigraphy is applied in the general population of hypertensive patients, a specificity of 0.90 will still yield a high proportion of false positive results, and a sensitivity of 0.70 means that almost a third of the patients will be missed. It is therefore clear that renal scintigraphy is not suitable for the screening of unselected hypertensive patients. In a preselected population with a higher prevalence of renal artery stenosis, a specificity of 0.90 may be acceptable, but the fact remains that a substantial number of patients with stenosis will be missed.

Some points of criticism may be raised. Firstly, about 50% of the patients in our study had renal artery stenosis, which illustrates that the studied population was in fact strongly selected. In computerized tests sensitivity and specificity are not influenced by the prevalence of a disease, contrary to positive predictive value and negative predictive value. In contrast, in tests in which a subjective interpretation determines part of the test outcome, it has been described that the prevalence of a disease can alter the diagnostic

properties of such a test: in circumstances of a higher prevalence, the physician will be more inclined to make a positive diagnosis.[1] In our study, this would lead to overestimation of the sensitivity, rather than underestimation. Our conclusion that renal scintigraphy is not useful as a screening test in unselected patients remains therefore a valid one.

The study described in **Chapter 2** does not assess the value of renal scintigraphy to predict the blood pressure response after revascularization. The patients in this study were not systematically followed. Some information on this isssue is presented in **Chapter 7**. In the patients randomized for balloon angioplasty, in whom angioplasty was technically successful, the blood pressure was compared between patients with an abnormal renal scintigram at the time of intervention and patients with a normal scintigram. There was no difference in blood pressure response between the 2 groups. Our data, therefore, produce no evidence that an abnormal scintigram predicts a favorable blood pressure response to intervention.

Chapter 3 describes the rationale and design of the study. Inherent to its design, this study gives no estimation of the countrywide prevalence of renal artery stenosis, for the following reasons: the DRASTIC study provides no information on what proportion of the general population of hypertensives is referred to the internist; the participating internists may not be representative for the whole group of internists in the Netherlands; and, it is not exactly known how many of the patients referred for hypertension were actually included. Although the protocol prescribed to register the patients who were not included and to record the reasons for non-inclusion, this was often not done.

As described in **Chapter 4**, 1205 patients were included in the diagnostic part of the DRASTIC study. In 72 patients a scintigraphic and/or angiographic diagnosis of renal artery stenosis had been made before enrolment. These patients were therefore excluded from the analyses on the diagnostic strategy. Of the 1106 patients with complete follow-up, 1022 could be assigned to one of the two standard drug regimens; 772 of these

were assigned by randomization. Medication consisted of one drug (amlodipine or enalapril) in patients ≤40 years and of two drugs (amlodipine with atenolol or enalapril with hydrochlorothiazide) in patients >40 years. In 55% of these patients blood pressure was adequately controlled with these regimens; these patients did not undergo further diagnostic work-up.

Drug-resistant hypertension, defined according to prespecified criteria, was identified in 41% of the patients and these patients underwent renal angiography. Twenty percent of them had renal artery stenosis. Renal function impairment was observed in 8% of the patients on ACE inhibitor, and these patients also underwent angiography; it was associated with a 46% prevalence of renal artery stenosis. In the patients randomized to the two standard drug regimens, the prevalence of renal artery stenosis did not differ between the amlodipine- and enalapril-based regimens. The patients who could not be randomized for the standard antihypertensive drug regimens because of previous adverse reactions or (relative) contra-indications to certain drugs, received one of the standardized regimens by choice. The non-randomized patients had a higher prevalence of renal artery stenosis than the randomized patients (35 vs 15%). This was to be expected, given the fact that the reasons for non-randomization included the presence of angina pectoris or claudication and an elevated serum creatinine, which are risk factors for renal artery stenosis.

Patients who had no drug-resistant hypertension did not undergo further diagnostic work-up. The sensitivity and specificity of drug-resistant hypertension could therefore not be studied; to assess sensitivity and specificity would have required the performance of angiography in every included patient. Because the prevalence of renal artery stenosis is highest in the patients with difficult-to-control hypertension, and because we argued that only these patients are justified candidates for intervention, the work-up was restricted to patients with difficult-to-treat hypertension. Patients with an additional clue to renal artery stenosis, that is patients who experienced renal function impairment after ACE inhibitor, were also investigated. We conclude from this study that selection on the basis of drug-resistant hypertension and ACE inhibitor-related renal function impairment is a practical and logical first step in the work-up for renal artery stenosis.

The use of standard drug regimens gives this study a somewhat artificial

character. On the other hand, the use of standard fixed-dose regimens has the important advantage that drug-resistance of the hypertension can be defined in an objective and reproducible way. In our opinion, extrapolation of our results to other antihypertensive drugs is possible by using the concept of the so-called daily defined dose (DDD). One DDD is the assumed average maintenance dose per day for a drug used on its main indication in adults.[2] This concept implies that one DDD of drug A can be compared with one DDD of drug B.

The following step in the development of an optimal diagnostic strategy was to investigate the predictive value of a number of clinical characteristics. This is described in **Chapter 5**. The difference with the study described in Chapter 4 is that only patients who underwent angiography were included. Age, the presence of atherosclerotic disease and serum creatinine were the most powerful predictors of renal artery stenosis. By combining these with 6 other readily available clinical characteristics, a prediction rule was constructed. A score was established for each characteristic separately. The total of these scores, the sum score, corresponds to predicted probability of renal artery stenosis for an individual patient. The accuracy of this model was similar to that of renal scintigraphy, with an area under the ROC curve of 0.84 (95% confidence interval, 0.79-0.89). This formula gives a quantitative approximation of probability. The physician can decide, on the basis of the predicted probability, whether or not to proceed to angiography in a given patient.

An important limitation in this study is the fact that the prediction rule was developed in a retrospective way using data of a selected patient population. This was inherent to the design of the study and it implies that further studies are needed to confirm the validity of the prediction rule in other settings.

Chapter 6 describes the interobserver variability in the assessment of renal angiograms. It shows poor agreement between three radiologists on the location of renal artery stenosis, ostial vs truncal. Ostial lesions show a higher rate of restenosis after angioplasty than truncal lesions, probably

because ostial stenoses are often part of an atherosclerotic plaque in the aortic wall. This is the rationale for treating ostial lesions with an arterial stent in addition to balloon dilatation, whereas the intervention in truncal lesions is mostly limited to dilatation alone. From our results, it can be concluded that other procedures, e.g. spiral CT angiography and MR angiography are necessary to visualize the stenosis more precisely.

The study shows good agreement about the question of whether a stenosis is present or not, e.g. <50% vs ≥50% lumen diameter reduction. However, when stenoses were classified into categories of 90%, 80%, 70% reduction etc. the agreement was poor. Improvement of interobserver agreement is perhaps possible by pre-arranging a standardized method for measuring the degree of stenosis or by computerized quantification of stenosis grade.

Although these results were not received with enthusiasm by radiologists, the data are highly relevant for the clinical approach of patients with atherosclerotic renovascular disease. Because of these findings, the discussion on what degree of stenosis on the angiogram should be considered as significant loses its ground. This discussion becomes even more complicated by findings of Gottsauner-Wolf et al.[3] They reported that many radiologists estimate the *area* stenosis, but describe this as *diameter* stenosis. In their study, coronary stenoses were assessed by computerized quantitative measurements as well as by visual evaluation from cine-film by a panel of three cardiologists. Although angiogram readers usually report their visual grading of stenosis as the reduction in lumen diameter (2-dimensional information), this study showed that the actual visual estimation corresponded better with the computerized measurements of surface area reduction (3-dimensional information). Apparently, the human eye automatically converts the observed percentage diameter stenosis into percentage area stenosis, taking into account other features such as length, symmetry, and the brightness of the dye in the area of the stenosis. The observer integrates this information even when he only wants to evaluate the difference between the tightest part of the stenosis and the reference diameter. This may have important implications; a 50% diameter stenosis for instance corresponds with a 75% area stenosis.

Chapter 7 compares the effect of balloon angioplasty with medication. This was studied in 106 patients with atherosclerotic renal artery stenosis; 56 patients were treated with balloon angioplasty with or without medication, and 50 with only medication. After 3 months, 22 patients of the medication group underwent angioplasty in second instance because of persistent high diastolic blood pressure or renal function impairment. There was no statistically significant difference in blood pressure between the two groups at 3 months, and at 12 months. After 1 year stenosis had recurred in about half of all patients who underwent angioplasty.

Cure of hypertension (diastolic blood pressure <95 mmHg without antihypertensive medication) was reached in only 7% of the patients of the angioplasty group. However, angioplasty appeared to have a medication-sparing effect. The blood pressure lowering capacity of balloon angioplasty corresponded with that of approximately one DDD of medication. The design of the study prescribed discontinuation of all antihypertensive drugs in patients randomized for balloon angioplasty. Medication was resumed, if blood pressure remained high despite the intervention. In contrast, in patients randomized for medication medical treatment was rather increased after randomization. The difference in the amount of medication between the angioplasty and the medication group at 3 months (2.1±1.3 vs 3.2±1.5 DDDs, $P<0.001$), is perhaps influenced by this difference in medical management. On the other hand, the fact remains that blood pressure in the angioplasty group was not higher despite the lesser dose of antihypertensive medication.

No difference in blood pressure response was observed between patients with and without restenosis or between patients with ≤ 70% and >70% stenosis. An abnormal scintigram at the time of inclusion was also not correlated with a better blood pressure response. The lack of an association between restenosis and blood pressure control has also been described by van de Ven et al,[4] in a randomized study on balloon dilatation vs stent placement. Despite a striking difference in the number of patent renal arteries in favor of the group treated with stent placement, blood pressure had not decreased more in this group than in the group treated with balloon dilatation without stenting.

One obvious drawback of our study is the fact that a substantial number

of patients randomized for medical treatment were treated with balloon angioplasty in second instance, thereby diluting a possible favorable effect of angioplasty. This type of design was chosen because at the time of enrolment balloon angioplasty was the treatment of choice in most centers. The ethics committee of the coordinating center criticized a previous version of the design, in which the patients of the medication group could undergo angioplasty not earlier than after 6 months. In spite of this drawback, the important point remains that the results at 12 months in the medication group were no worse than those in the patients randomized for angioplasty. The present study, therefore, does not argue against the more conservative treatment strategy that was followed in the patients randomized for medication, ie, extension of drug treatment and proceeding to balloon angioplasty only if after 3 months the patient is either hypertensive on ≥3 drugs, or shows evidence of renal function impairment.

Renal function after 3 months was slightly better in the angioplasty group than in the medication group. This difference failed to be statistically significant at 12 months. Improvement of the renal scintigram occurred more often after angioplasty than during medication and this effect remained present throughout the study period. Although the study was not designed to assess an effect on renal function, the results raise the possibility that angioplasty can preserve renal function.

In conclusion, balloon angioplasty has little advantage over medication in the treatment of hypertension associated with atherosclerotic renal artery stenosis. The effect on parameters of renal function suggest that angioplasty may prevent renal function impairment, but these results need to be confirmed by more definite endpoints during longer follow-up.

Do these results have an impact on the strategy to diagnose renal artery stenosis? The disappointing effect of balloon angioplasty on blood pressure could lead to diagnostic nihilism: why should we try to identify patients with renal artery stenosis when there is no adequate therapy for it? In this respect, two considerations have to be made: (1) Preliminary findings of the DRASTIC study suggest that the duration of hypertension was one of the few predictors of a favorable outcome after intervention.[5] Therefore, it may well be that balloon angioplasty is more successful in patients with recently developed hypertension; (2) A randomized study with renal function as the

major endpoint comparing angioplasty (with stent placement) to a conservative (medical) approach has not been performed. For the moment, the search for renal artery stenosis can still be defended with preservation of renal function as the major goal.

Does this study necessitate to change the search for renal artery stenosis into a search for renovascular hypertension? The traditional definition of renovascular hypertension as "hypertension that is improved after relief of the stenosis" has some major flaws. Firstly, technical failure or relapse of a stenosis prevents improvement of hypertension, whereas the stenosis could have been functionally significant, i.e. it caused the hypertension to develop. A second, different problem with this definition is the development of phase III Goldblatt hypertension.[6] In experimental models relief of the stenosis in this phase of renovascular hypertension does not reduce blood pressure, probably due to hypertension-induced changes in the contralateral kidney. If this phenomenon is present in humans, which has never been proven, it would prevent improvement of hypertension after intervention, whereas the stenosis had been in fact functionally significant. Therefore we advocate to study both the treatment of the anatomic renal artery stenosis, as well as the factors that determine the cause and the reversibility of renovascular hypertension, in order to develop a definition that can be used in clinical practice.

Recommendations for clinical practice

For the diagnostic and therapeutic approach of patients with renal artery stenosis, we would give the following recommendations:

1) Perform diagnostic work-up when the patients' blood pressure remains high despite treatment with ≥2 drugs
2) Perform angiography in patients with a probability of renal artery stenosis >50% according to the prediction rule
3) In patients with a probability of renal artery stenosis of 10-50% angiography can be replaced by magnetic resonance angiography or spiral CT angiography. In patients with risk factors for radiocontrast toxicity, or when MRA is not possible or available, angiography or renal scintigraphy can be chosen.
4) In patients with a probability of renal artery stenosis <10% according to the prediction rule no further diagnostic work-up is warranted.
5) In patients with ACE inhibitor treatment-related renal function impairment proceed to renal angiography without prior tests.
6) Hypertensive patients with a renal artery stenosis caused by atherosclerosis have to be treated with angioplasty (if necessary with additional stent placement)
   a) when there is hypertension that can not be controlled with 3 drugs,
   b) when there is evidence of renal function impairment, or
   c) when the renal artery lumen is almost occluded.

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NEDERLANDSE SAMENVATTING

Het onderzoek beschreven in dit proefschrift is verricht (1) om een optimale strategie te ontwikkelen voor de diagnose nierarteriestenose, en (2) om het effect van ballonangioplastiek op de bloeddruk na te gaan bij patiënten met een atherosclerotische nierarteriestenose. In dit hoofdstuk worden de sterke en zwakke punten van de verschillende onderdelen van het onderzoek besproken, en worden de belangrijkste conclusies samengevat. Ook worden enkele praktische aanbevelingen geformuleerd.

De diagnostische nauwkeurigheid van nierscintigrafie bleek teleurstellend te zijn, zoals wordt beschreven in **Hoofdstuk 2**. Bij een specificiteit van 0.90, hetgeen naar onze mening minimaal vereist is, was de sensitiviteit slechts 0.65 voor DTPA scintigrafie zonder captoprilprovocatie en 0.68 voor DTPA scintigrafie na captoprilprovocatie. "Receiver operating characteristic" (ROC) curves werden geconstrueerd voor de fractionele opname van één nier (ook genoemd links-rechts verhouding) als diagnostische parameter. De ROC curves voor DTPA scintigrafie met en zonder captoprilprovocatie waren vergelijkbaar, hetgeen aangeeft dat het gebruik van captopril geen voordelen biedt. MAG_3 scintigrafie was niet beter dan DTPA scintigrafie wat betreft de diagnostische nauwkeurigheid, terwijl het moeilijker is een MAG_3 scintigram te beoordelen dan een DTPA scintigram.

Wanneer nierscintigrafie wordt gebruikt in de algemene populatie van hypertensiepatiënten, zal een specificiteit van 0.90 nog steeds een groot percentage fout-positieve uitkomsten opleveren, terwijl een sensitiviteit van 0.70 betekent dat bijna eenderde van de patiënten met nierarteriestenose niet herkend wordt. Nierscintigrafie is dan ook niet geschikt voor de screening van ongeselecteerde patiënten met hypertensie. Bij een voorgeselecteerde populatie met een hogere prevalentie van nierarteriestenose zou een specificiteit van 0.90 acceptabel zijn, maar dan blijft staan dat een aanzienlijk deel van de patiënten met stenose gemist wordt.

Enkele punten van kritiek kunnen worden geopperd. Ten eerste, ongeveer 50% van de patiënten in onze studie had nierarteriestenose, hetgeen illustreert dat de onderzochte populatie al sterk geselecteerd was. Bij

geautomatiseerde tests worden de sensitiviteit en specificiteit niet benvloed door de prevalentie van een aandoening, in tegenstelling tot positief-voorspellende waarde en negatief-voorspellende waarde. Daartegenover staat dat bij tests waarbij de testuitslag deels bepaald wordt door subjectieve interpretatie, de prevalentie van een aandoening de diagnostische eigenschappen van zo'n test kan veranderen: als de prevalentie van een ziekte hoger is, zal degene die de test beoordeelt meer geneigd zijn tot een positieve diagnose.[1] In onze studie zou dit fenomeen eerder tot overschatting van de sensitiviteit leiden, dan tot onderschatting. Onze conclusie dat nierscintigrafie niet bruikbaar is als screeningstest bij ongeselecteerde patiënten blijft daarom valide.

De studie beschreven in **Hoofdstuk 2** geeft geen informatie over de waarde van nierscintigrafie bij het voorspellen van de bloeddrukdaling na revascularisatie. De patiënten werden niet systematisch genoeg gevolgd om hierover een uitspraak te doen. Wel komen gegevens over dit onderwerp naar voren in **Hoofdstuk 7**. Bij de patiënten gerandomiseerd voor ballonangioplastiek, bij wie de procedure technisch uitvoerbaar was, werd de bloeddruk vergeleken van patiënten met een afwijkend scintigram op het tijdstip van interventie en patiënten met een normaal scintigram. Er was geen verschil in bloeddrukdaling tussen deze twee groepen. Onze gegevens geven dan ook geen steun aan de veronderstelling dan een afwijkend scintigram kan voorspellen of de bloeddruk gunstig reageert op een interventie. Wel lijkt het scintigram bruikbaar voor de follow-up van patiënten die interventie ondergingen, omdat een verslechtering van het scintigram progressie van de stenose lijkt te voorspellen.

Hoofdstuk 3 beschrijft de beweegreden en de opzet van de studie. De opzet van de studie is zodanig dat geen schatting mogelijk is van de landelijke prevalentie van nierarteriestenose, om de volgende redenen: de "Dutch Renal Artery Stenosis Intervention Cooperative" (DRASTIC) studie verschaft geen informatie over de proportie van de algemene populatie van hypertensiepatiënten die naar de internist wordt verwezen; het is onduidelijk of de participerende internisten representatief zijn voor het totaal aan internisten in Nederland; en tenslotte is niet precies bekend welk percentage van de patiënten, die verwezen werden vanwege hypertensie, ook

daadwerkelijk werd geïncludeerd. Hoewel het protocol voorschreef om het aantal patiënten dat niet werd geïncludeerd te registreren, alsmede de redenen hiervoor, is dit helaas niet systematisch gedaan.

Zoals beschreven in **Hoofdstuk 4** werden 1205 patiënten geïncludeerd in de diagnostische fase van de DRASTIC-studie. Bij 72 patiënten werd de diagnose nierarteriestenose reeds gesteld vòòr inclusie door middel van scintigrafie en/of angiografie. Deze patiënten werden dan ook niet betrokken bij de analyses over de diagnostische strategie. Van de 1106 patiënten met een complete follow-up werd aan 1022 patiënten één van de twee standaard medicatieregimes voorgeschreven; bij 772 van hen geschiedde dit via randomisatie. De medicatieregimes bestonden uit één middel (amlodipine of enalapril) bij patiënten ≤40 jaar en uit 2 middelen (amlodipine met atenolol of enalapril met hydrochloorthiazide) bij patiënten > 40 jaar. Bij 55% van deze patiënten kon de hypertensie afdoende worden behandeld met deze regimes; deze patiënten ondergingen geen verdere diagnostiek.

Therapieresistente hypertensie, gedefinieerd volgens tevoren vastgestelde criteria, was aanwezig bij 41% van de patiënten en deze patiënten ondergingen angiografie van de nierarteriën. Twintig procent van hen had nierarteriestenose. Nierfunctieverslechtering was aanwezig bij 8% van de patiënten die behandeld werden met een "angiotensin converting enzyme" (ACE) remmer, en ook deze patiënten ondergingen angiografie; hier bedroeg de prevalentie van nierarteriestenose 46%. Bij de patiënten die gerandomiseerd waren voor de twee standaard medicatieregimes, verschilde de prevalentie van nierarteriestenose tussen het amlodipine- en het enalapril-regime niet. De patiënten die niet gerandomiseerd konden worden voor de standaard antihypertensieve medicatieregimes vanwege bijwerkingen of (relatieve) contra-indicaties, werden behandeld met een van de medicatieregimes naar keuze. Deze niet-gerandomiseerde patiënten hadden een hogere prevalentie van nierarteriestenose dan de gerandomiseerde patiënten (35 vs 15%). Dit was ook te verwachten, omdat de redenen waarom patiënten niet gerandomiseerd konden worden, zelf risicofactoren voor nierarteriestenose waren, b.v. angina pectoris, claudicatio intermittens en een verhoogd serumcreatinine.

Patiënten zonder therapieresistente hypertensie ondergingen geen diagnostische work-up. De sensitiviteit en specificiteit van het criterium therapieresistente hypertensie konden daarom niet worden vastgesteld; dit zou hebben vereist dat bij elke geïncludeerde patiënt angiografie van de nierarteriën zou zijn verricht. Omdat de prevalentie van nierarteriestenose het hoogst is bij patiënten met moeilijk te behandelen hypertensie, èn omdat we van mening waren dat alleen deze patiënten kandidaten waren voor een eventuele interventie, werd de work-up beperkt tot patiënten met moeilijk te behandelen hypertensie. Patiënten met een extra aanwijzing voor nierarteriestenose, namelijk patiënten die een nierfunctieverslechtering toonden tijdens behandeling met een ACE-remmer, werden ook onderzocht. We concluderen uit deze studie dat selectie op basis van therapieresistente hypertensie en ACE-remmer-gerelateerde nierfunctieverslechtering een praktische en logische eerste stap is bij de diagnostiek naar nierarteriestenose.

Het gebruik van de standaard medicatieregimes geeft deze studie een enigszins gekunsteld karakter. Echter, het gebruik van standaard regimes in een vaste dosis heeft het belangrijke voordeel dat therapieresistentie objectief en reproduceerbaar kan worden gedefinieerd. Naar onze mening is extrapolatie van onze resultaten naar andere antihypertensiva mogelijk door het gebruik van het concept van de zogenoemde dagelijkse standaarddosis (defined daily dose; DDD). Eén DDD is de veronderstelde gemiddelde onderhoudsdosis per dag voor een medicament dat gebruikt wordt voor z'n belangrijkste indicatie bij volwassenen.[2] Dit concept impliceert dat 1 DDD van middel A kan worden vergeleken met 1 DDD van middel B.

De volgende stap bij de ontwikkeling van een optimale diagnostische strategie was het onderzoeken van de voorspellende waarde van een aantal klinische kenmerken. Dit wordt beschreven in **Hoofdstuk 5**. Het verschil met de studie van Hoofdstuk 4 is dat nu alleen patiënten werden geïncludeerd die angiografie ondergingen. Leeftijd, de aanwezigheid van atherosclerotisch vaatlijden en het serumcreatinine waren de krachtigste voorspellers van nierarteriestenose. Door deze te combineren met 6 andere makkelijk te vergaren klinische kenmerken werd een predictieregel geconstrueerd. Voor elk van de afzonderlijke kenmerken werd een score

vastgesteld. Het totaal van deze scores, de somscore, correspondeert met een voorspelde kans op nierarteriestenose voor een individuele patiënt. De nauwkeurigheid van dit model was vergelijkbaar met dat van nierscintigrafie. De predictieregel biedt een kwantitatieve benadering van de kans dat nierarteriestenose aanwezig is. De clinicus kan bepalen, op basis van deze voorspelde kans, of het verstandig is bij een bepaalde patiënt al dan niet angiografie te verrichten.

Een belangrijke beperking van deze studie is het feit dat de predictieregel ontwikkeld werd in een retrospectief model, gebruikmakend van data van een geselecteerde patiëntenpopulatie. Dit was inherent aan de studie-opzet, en het impliceert dat toekomstige studies nodig zijn om de validiteit van de predictieregel in andere populaties te bevestigen.

Hoofdstuk 6 beschrijft de interobserver variabiliteit bij het beoordelen van een angiogram van de nierarteriën. Er blijkt slechte overeenstemming te zijn tussen 3 radiologen bij de beoordeling van de plaats van de nierarteriestenose, in het ostium of in de truncus van de niertarterie. Ostiumlaesies vertonen een grotere kans op een recidief stenose na angioplastiek dan truncuslaesies, waarschijnlijk omdat ostiumlaesies vaak onderdeel zijn van een atherosclerotische plaque in de aortawand. Dit is de achtergrond voor de voorkeur voor stentplaatsing bij ostiumlaesies, terwijl de interventie bij truncuslaesies meestal beperkt blijft tot dilatatie. Uit onze resultaten kan geconcludeerd worden dat andere onderzoeksmethoden, b.v. spiraal CT angiografie en MR angiografie, noodzakelijk zijn om de stenose preciezer in beeld te brengen.

De studie toont goede overeenstemming tussen de radiologen over de vraag of er al dan niet een stenose aanwezig is, b.v. <50% vs ≥50% reductie van de lumendiameter. Echter, als de stenosen geclassificeerd werden in categorieën van 90%, 80%, 70%, etc. reductie was de overeenstemming slecht. Verbetering van overeenstemming tussen waarnemers is wellicht mogelijk door tevoren een gestandaardiseerde methode voor het meten van de stenosegraad af te spreken, of door kwantificering van de stenosegraad via een computersysteem.

Hoewel deze resultaten niet met enthousiasme werden begroet in de radiologische wereld, zijn de data bijzonder relevant voor de klinische

benadering van patiënten met atherosclerotisch niervaatlijden. Door deze bevindingen komt de discussie over de significantie van de stenosegraad op het angiogram op losse schroeven. Deze discussie wordt nog gecompliceerder door de bevindingen van Gottsauner-Wolf et al.[3] Zij beschreven dat veel radiologen het stenose-*oppervlak* schatten, maar dit beschrijven als stenose-*diameter*. In hun studie werden stenosen in de coronairarteriën geëvalueerd door kwantitatieve metingen met behulp van een computer, maar ook door visuele evaluatie van de cine-film door een panel van 3 cardiologen. Hoewel waarnemers van een angiogram hun inschatting van de stenosegraad meestal inschatten als de reductie in lumendiameter (2-dimensionele informatie), toonde deze studie dat de visuele schatting beter correspondeerde met de computermetingen van de reductie van het oppervlak van het bloedvat ter plaatse van de stenose (3-dimensionele informatie). Blijkbaar converteert het menselijk oog het waargenomen percentage diameter-stenose in percentage oppervlakte-stenose, daarbij rekening houdend met andere factoren zoals lengte, symmetrie en de helderheid van het contrast in het gebied van de stenose. De waarnemer integreert deze informatie zelfs als hij alleen het verschil tussen het nauwste deel van de stenose en de referentiediameter wil evalueren. Dit verschijnsel heeft belangrijke implicaties: 50% diameter-stenose correspondeert b.v. met 75% oppervlakte-stenose.

In **Hoofdstuk** 7 wordt het effect van ballonangioplastiek vergeleken met dat van medicatie. De studie werd verricht bij 106 patiënten met een atherosclerotische nierarteriestenose; 56 patiënten werden behandeld met ballonangioplastiek met of zonder medicatie, en 50 met alleen medicatie. Na 3 maanden ondergingen 22 patiënten uit de medicatiegroep in tweede instantie angioplastiek vanwege een persisterend hoge bloeddruk of nierfunctieverslechtering. Er was geen statistisch significant verschil in bloeddruk tussen de 2 groepen na 3 maanden, noch na 12 maanden. Na 12 maanden was de stenose teruggekomen bij ongeveer de helft van alle patiënten die angioplastiek ondergingen. Genezing van hypertensie (diastolische bloeddruk < 95 mmHg zonder antihypertensieve medicatie) werd bij slechts 7% van de patiënten uit de angioplastiekgroep bereikt. Echter, ballonangioplastiek bleek een medicatiesparend effect te hebben.

Het bloeddrukverlagende vermogen van ballonangioplastiek correspondeerde met ongeveer 1 DDD aan medicatie, omdat de patiënten in de angioplastiekgroep ongeveer 1 DDD medicatie minder gebruikten dan de medicatiegroep om dezelfde bloeddruk te bereiken. De opzet van de studie schreef voor dat alle antihypertensiva moesten worden gestaakt bij patiënten gerandomiseerd voor ballonangioplastiek. Medicatie werd hervat als de bloeddruk hoog bleef ondanks de interventie. Aan de andere kant, bij patiënten gerandomiseerd voor medicatie werd de medicamenteuze behandeling van de hypertensie juist uitgebreid na randomisatie. Het verschil in de hoeveelheid medicatie tussen de angioplastiek- en de medicatiegroep bij 3 maanden (2.1 ±1.3 vs 3.2 ±1.5 DDDs, $p<0.001$), wordt wellicht beïnvloed door dit verschil in aanpak. Hoe dan ook, het feit blijft dat de bloeddruk in de angioplastiekgroep niet hòger was ondanks de lagere dosis aan antihypertensieve medicatie.

Er werd geen verschil in bloeddrukdaling geconstateerd tussen patiënten met en zonder restenose, en ook niet tussen patiënten met ≤70% en >70% stenose. Een afwijkend scintigram op het tijdstip van inclusie was evenmin gecorreleerd met een sterkere bloeddrukdaling. Het ontbreken van een verband tussen restenose en bloeddrukdaling is ook beschreven door van der Ven et al.[4] in een gerandomiseerd onderzoek naar ballondilatatie vs. stentplaatsing. Ondanks een opvallend verschil in het aantal doorgankelijke nierarteriën ten gunste van de groep patiënten die met stentplaatsing werd behandeld, daalde de bloeddruk niet sterker in deze groep dan in de groep patiënten behandeld met ballonangioplastiek zonder stentplaatsing.

Een onmiskenbaar bezwaar van deze studie is het feit dat een aanzienlijk aantal patiënten dat gerandomiseerd was voor medicamenteuze behandeling, alsnog werd behandeld met ballonangioplastiek, waardoor een mogelijk gunstig effect van ballonangioplastiek verdund wordt. Een dusdanige opzet werd gekozen omdat in de periode van patiënteninclusie ballonangioplastiek de behandeling van eerste keuze was in de meeste ziekenhuizen. De ethische commissie van het coördinerende ziekenhuis bekritiseerde zelfs een eerdere versie van de studie-opzet, waarin de patiënten van de medicatiegroep pas na 6 maanden ballonangioplastiek konden ondergaan. Ondanks dit nadeel, blijft een belangrijk punt overeind: na 12 maanden waren de resultaten in de medicatiegroep niet slechter dan die van de

patiënten gerandomiseerd voor ballonangioplastiek. De studie ondersteunt daarmee de meer conservatieve behandelingsstrategie die gevolgd werd bij de patiënten gerandomiseerd voor medicatie, namelijk uitbreiding van medicamenteuze behandeling en alleen de overgang naar ballonangioplastiek als de patiënt na 3 maanden nog steeds hypertensief is bij ≥ 3 middelen, of aanwijzingen toont voor nierfunctieverval.

Na 3 maanden was de nierfunctie iets beter in de angioplastiekgroep dan in de medicatiegroep. Dit verschil was niet statistisch significant na 12 maanden. Na ballonangioplastiek werd vaker verbetering van het nierscintigram waargenomen dan bij behandeling met medicatie en dit effect bleef aanwezig gedurende de hele studie. Hoewel de studie niet was opgezet om het effect van ballonangioplastiek op de nierfunctie te onderzoeken, wekken de resultaten de suggestie dat ballonangioplastiek een preserverend effect heeft op de nierfunctie.

Concluderend, ballonangioplastiek heeft weinig voordeel boven medicatie bij de behandeling van hypertensie geassocieerd met atherosclerotische nierarteriestenose. Het effect op parameters van de nierfunctie suggereert dat ballonangioplastiek nierfunctieverslechtering kan voorkomen, maar deze resultaten moeten met hardere eindpunten worden bevestigd gedurende een langere follow-up.

Hebben deze resultaten consequenties voor de diagnostiek van nierarteriestenose? Het teleurstellende effect van ballonangioplastiek op de bloeddruk zou kunnen leiden tot diagnostische nihilisme: waarom zouden we proberen om patiënten met nierarteriestenose te identificeren als er geen adequate behandeling voorhanden is? Hieromtrent, moet men twee zaken in ogenschouw nemen: (1) Voorlopige bevindingen van de DRASTIC-studie suggereren dat de bestaansduur van de hypertensie een van de weinige voorspellers was van een gunstig effect van de interventie; daarom zou ballonangioplastiek effectiever kunnen zijn bij patiënten met hypertensie die recent ontstaan is.[5] (2) Er is nooit een gerandomiseerde studie verricht met nierfunctie als belangrijkste eindpunt, waarin ballonangioplastiek (eventueel met stentplaatsing) werd vergeleken met een medicamenteuze aanpak. Het zoeken naar nierarteriestenose kan dan ook verdedigd worden, met het behoud van nierfunctie als belangrijkste therapeutisch einddoel.

Geeft deze studie aanleiding om niet langer te zoeken naar

nierarteriestenose maar naar renovasculaire hypertensie? De klassieke definitie van renovasculaire hypertensie als "hypertensie die verbetert na het opheffen van de stenose" heeft grote tekortkomingen. Ten eerste, technisch falen of een recidief van de stenose zal verbetering van hypertensie tegenhouden, terwijl de stenose wel "functioneel" kan zijn geweest, dat wil zeggen dat de stenose de hypertensie veroorzaakte. Een tweede, ander probleem met deze definitie is de ontwikkeling van fase III Goldblatt hypertensie.[6] In diermodellen leidt opheffen van de stenose in deze fase van renovasculaire hypertensie niet tot een reductie van de bloeddruk, waarschijnlijk als gevolg van hypertensie-geïnduceerde veranderingen in de contralaterale nier door langdurige hypertensie. Als dit fenomeen ook bij de mens aanwezig is, hetgeen nooit bewezen is, zou dit verbetering van de hypertensie na interventie voorkomen, terwijl de stenose wel functionele betekenis had. Daarom pleiten wij ervoor om zowel de behandeling van de anatomische nierarteriestenose te bestuderen, als de factoren die de oorzaak en de omkeerbaarheid van renovasculaire hypertensie bepalen in de hoop ooit een definitie op te stellen die bruikbaar is voor de klinische praktijk.

Aanbevelingen

Wat betreft de diagnostische en therapeutische benadering van patiënten met nierarteriestenose zouden wij de volgende aanbevelingen willen geven:

1) Verricht diagnostiek naar nierarteriestenose als de bloeddruk van de patiënt hoog blijft ondanks behandeling met ≥ 2 middelen.
2) Verricht direct angiografie bij patiënten met een kans op nierarteriestenose van 50% volgens de predictieregel.
3) Bij patiënten met een kans op nierarteriestenose van 10-50% kan angiografie worden vervangen door MR angiografie of spiraal CT angiografie. Als er risicofactoren zijn voor contrasttoxiciteit, of als MR angiografie niet mogelijk of niet beschikbaar is, kan men kiezen voor angiografie of nierscintigrafie.
4) Geen diagnostiek is geïndiceerd bij patiënten met een kans op nierarteriestenose van 10% volgens de predictieregel.
5) Verricht direct angiografie bij patiënten met ACE-remmer gerelateerde nierfunctieverslechtering.
6) Bij patiënten met hypertensie en een atherosclerotische nierarteriestenose is ballonangioplastiek (eventueel met stentplaatsing) geïndiceerd
   a) als de hypertensie niet met 3 middelen onder controle te brengen is
   b) als er aanwijzingen zijn voor nierfunctieverslechtering
   c) als het arterielumen bijna geoccludeerd is.

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NAWOORD

Het vaststellen van de promotiedatum is als het boven water komen na een lange tocht onder water zwemmen. Ook al vergden de laatste loodjes nog een hernieuwde duik, ik blijf nu voorlopig even bòven.

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CURRICULUM VITAE

Brigit van Jaarsveld werd geboren op 13 maart 1961 in Zeddam (Gld). Zij bezocht het St. Bonifatiuscollege in Utrecht en studeerde medicijnen eveneens in Utrecht. Na een jaar werkzaam te zijn geweest op de afdeling Longziekten van het Catharina Ziekenhuis, volgde zij de opleiding tot internist in het Elisabeth Ziekenhuis in Amersfoort (Dr. R.A. Geerdink) en in het Academisch Ziekenhuis Utrecht (Prof.Dr. A. Struyvenberg, Prof.Dr. D.W. Erkelens). Vanaf 1993 werkte zij aan het onderwerp van dit proefschrift vanuit de afdeling Interne Geneeskunde I van het Dijkzigt Ziekenhuis te Rotterdam. Vanaf 1998 werd zij opgeleid voor het aandachtsgebied nefrologie (Prof.Dr. W. Weimar). Per 1 september 1999 is zij werkzaam als internist-nefroloog bij Stichting Dianet, lokatie Utrecht.

Zij is voor het leven contractueel verbonden aan Kees van Essen, en moeder van Trui en Kees.